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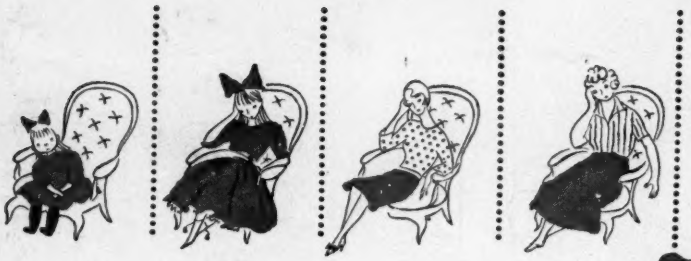
Beginning with the October 1950 issue, it is planned to introduce several changes in the covers of all the A. M. A. specialty journals.

The cover of this journal will be white enamel stock with title identification as the A. M. A. Archives of Internal Medicine in color, with date, volume and number also in color. The Table of Contents, which is now carried on the back cover, will be placed in the front of the journal directly preceding the lead article or editorial. Second, third and fourth covers will be used for color advertising.



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1. "A Method of Improving Function of the Bowel": J. Arnold Bargen, M.D., Division of Medicine, Mayo Clinic, Rochester, Minnesota, in Gastroenterology, 13:275 (Oct.) 1949.

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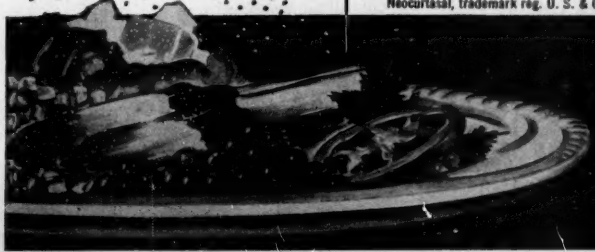

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2. Bell, George O., Bradley, Robert B., and Hurxthal, Lewis M. Paroxysmal Tachycardia: Experiences with Massive Doses of Quinidine Intravenously in a Refractory case. Circulation 1 — 939 - 969 (April, Part II) 1950.

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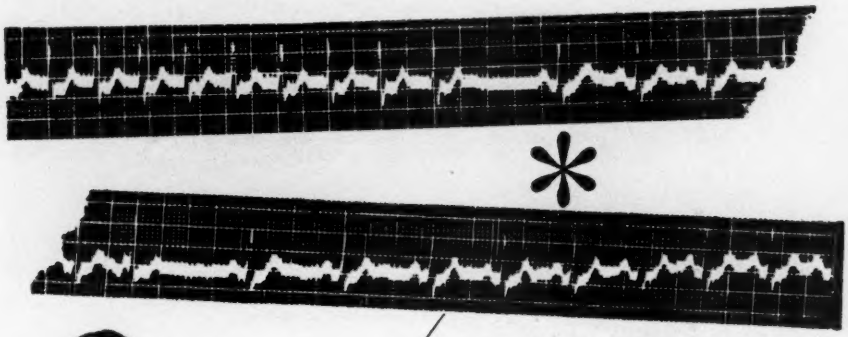

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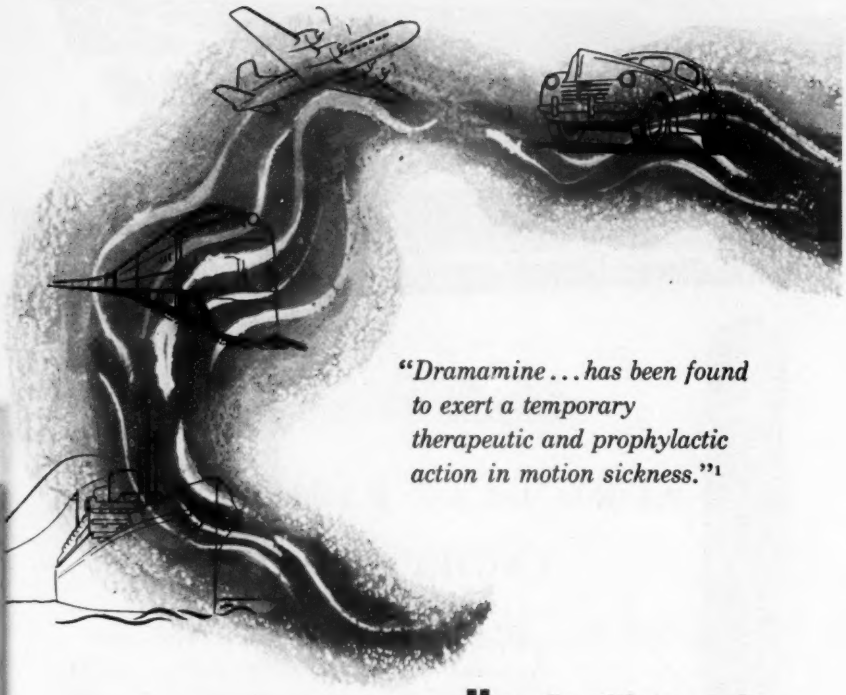

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1. Council on Pharmacy & Chemistry: New and Non-official Remedies, 1950, Philadelphia, J. B. Lippincott Co., 1950, p. 460.

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SEARLE RESEARCH IN THE SERVICE OF MEDICINE

ARCHIVES of INTERNAL MEDICINE

VOLUME 86 SEPTEMBER 1950 NUMBER 3

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CLINICAL STUDIES WITH ACTH AND CORTISONE IN RENAL DISEASE

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THE DEVASTATING effects of glomerular nephritis and the considerable disability induced by this disease are well known. The fact that nephritis has a predilection for children and young adults serves as an additional stimulus to the search for a means of controlling the disease. To date, therapy is limited to procedures which ameliorate the metabolic abnormalities secondary to renal failure or attempts to reduce the incidence of intercurrent infections. The dramatic effect which pituitary adrenocorticotropic hormone (ACTH) and cortisone [1] exert on the course of a wide variety of systemic diseases of unknown origin, especially those in which an antigen-antibody type of reaction is believed to play an important etiologic role, stimulated us to investigate the possible beneficial effect of these hormones in patients with glomerular

From the Department of Medicine, Harvard Medical School, and the Medical Clinic, Peter Bent Brigham Hospital.

This investigation was supported by a research grant from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

1. Hench, P. S.; Kendall, E. C.; Slocumb, C. H., and Polley, H. F.: The Effect of a Hormone of the Adrenal Cortex (17-Hydroxy-11-Dehydrocorticosterone: Compound E) and of Pituitary Adrenocorticotropic Hormone on Rheumatoid Arthritis; Preliminary Report, Proc. Staff Meet., Mayo Clin. **24**:181, 1949. Thorn, G. W.; Forsham, P. H.; Frawley, T. F.; Hill, S. R., Jr.; Roche, M.; Staehelin, D., and Wilson, D. L.: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783 and 824, 1950.

nephritis. Furthermore, earlier studies [2] indicating an apparent competitive inhibition of cortisone on excessive sodium retention induced by desoxycorticosterone naturally suggested an investigation of these phenomena in patients with nephrotic edema.

Sporadic attempts to modify the course of subacute nephritis met with little success initially. It was clearly evident that the response of patients with glomerular nephritis was far different from that observed in patients with rheumatic fever, rheumatoid arthritis, disseminated lupus erythematosus and certain allergic disorders. However, we were stimulated to study the problem more thoroughly by the enthusiastic report of Farnsworth.[3]

MATERIAL AND METHODS

CLINICAL MATERIAL

In selecting cases for this study, it was appreciated that a high proportion of patients with acute glomerulonephritis undergo a relatively rapid, spontaneous

TABLE 1.—*Use of Adrenal Hormones in Renal Disease: Summary of Clinical Material*

Diagnosis	No. of Cases	Type of Treatment	No. of Patients
Acute glomerular nephritis	4	ACTH	4
Subacute and chronic glomerular nephritis	7	ACTH	4
		Cortisone	3
Nephrotic syndrome	6	ACTH	4
		Cortisone	2
Nephritis of disseminated lupus	6	ACTH	6
Nephritis of dermatomyositis	3	ACTH	3

recovery. It also appeared evident that the late stage of chronic glomerulonephritis with advanced renal failure probably represented an irreversible phase of the disease. For these reasons the majority of the patients in this study were selected from groups representing either subacute glomerulonephritis with hematuria or chronic glomerulonephritis with the nephrotic syndrome without significant nitrogen retention. A few patients with acute nephritis and in the late stage of chronic nephritis were investigated, as well as patients with disseminated lupus and dermatomyositis undergoing prolonged ACTH or cortisone therapy (table 1).

METHODS

All patients undergoing balance studies were maintained in the metabolic unit of the Peter Bent Brigham Hospital throughout the period of study. Patients were kept on a constant diet during balance studies, and twenty-four hour urine specimens were collected. When 17-ketosteroid collections were made, 15 drops

2. Forsham, P. H.; Flink, E. B.; Emerson, K., Jr., and Thorn, G. W.: Metabolic Studies in Cushing's Syndrome, J. Clin. Investigation **28**:781, 1949.

3. Farnsworth, E. B.: Studies on the Influence of Adrenocorticotropin in Acute Nephritis, in Simple Nephrosis and in Nephrosis with Azotemia, in Mote, J. R.: Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Company, 1950, p. 297.

of 50 per cent sulfuric acid solution was added to the twenty-four hour bottle before beginning the collection. The semiquantitative measurement of formed elements excreted in the urine was made by the new method of Addis.[4] Fresh urine specimens were collected over a known period and examined for each patient by the same observer. All but 0.5 ml. of this specimen was added to the twenty-four hour collection subsequently. Following the day of collection, all specimens were stored at 4 C. (39.2 F.). The basal metabolic rate was determined with a closed circuit apparatus of the Roth-Benedict type; the accumulation gradient of radioactive iodine (I^{131}) was determined by the direct counting method over the thyroid as describd by Astwood and Stanley.[5]

Hematologic and blood chemical studies were made on venous blood taken in the preabsorptive state with minimal stasis. The anticoagulants used varied with the particular purpose, including balanced oxalate solution for the hematologic specimens,[6] and a mixture of potassium oxalate and fluoride for blood sugar determinations. Serum was obtained within thirty minutes after drawing the sample, extreme care being taken to avoid hemolysis.

Standard hematologic technics were employed.[6] Circulating eosinophils were enumerated by a modification of the method of Dunger.[7]

The following chemical methods were employed in this study: Sodium and potassium were determined with a flame photometer by the internal lithium standard method[8]; chloride by the mercurometric titration method of Schales and Schales,[9] with the modification of Asper[10] being used for urine specimens; inorganic phosphorus by the method of Fiske and Subbarow[11]; calcium by the method of Clark and Collip[12]; serum carbon dioxide–combining power by the Van Slyke manometric technic[13]; total urinary nitrogen by the Keys micro-Kjeldahl procedure[14]; serum total protein by Van Slyke's copper sulfate method[15] and

4. Addis, T.: Glomerular Nephritis: Diagnosis and Treatment, New York, The Macmillan Company, 1949.

5. Astwood, E. B., and Stanley, M. M.: Use of Radioactive Iodine in the Study of Thyroid Function in Man, West. J. Surg. **55**:625, 1947.

6. Wintrobe, M. M.: Clinical Hematology, ed. 2, Philadelphia, Lea & Febiger, 1946.

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8. Berry, J. W.; Chappell, D. G., and Barnes, R. B.: Improved Method of Flame Photometry, Indust. & Engin. Chem. **18**:19, 1946.

9. Schales, O., and Schales, S. S.: A Simple and Accurate Method for the Determination of Chloride in Biological Fluids, J. Biol. Chem. **140**:878, 1941.

10. Asper, S. P.; Schales, O., and Schales, S. S.: Importance of Controlling p_H in the Schales and Schales Method of Chloride Determination, J. Biol. Chem. **168**: 779, 1947.

11. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**:375, 1925.

12. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461, 1925.

13. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Co., 1932, vol. 2, p. 296.

14. Keys, A.: A Rapid Micro-Kjeldahl Method, J. Biol. Chem. **132**:181, 1940.

15. Peters and Van Slyke,[13] p. 941.

the method of Daly[16]; albumin to globulin ratios by the method of Howe[17]; blood urea nitrogen by the method of Archibald[18] and urinary urea nitrogen by the hypobromite technic[19]; blood glucose by the method of Folin and Wu,[20] using the Somogyi zinc hydroxide precipitation[21]; cholesterol, both free and total, by a modification of the method of Schoenheimer and Sperry[22]; creatine by the method of Lambert[23]; creatinine by the method of Folin[20]; uric acid in serum and urine by a modification of the method of Kern and Stransky,[24] and 17-ketosteroids by a modification of the method of Callow, Callow and Emmens,[25] with a suitable color correction for chromogens.[26]

OBSERVATIONS

I. ACUTE GLOMERULAR NEPHRITIS

Four patients with acute glomerular nephritis were treated with ACTH[27] (table 2).

Case 1.—Two weeks before his admission, D. W., a boy 8 years of age, had mild pharyngitis, followed one week later by recurrent sore throat and cervical adenitis. Five days before admission the urine was noted to be smoky. He was treated with sulfadiazine and penicillin. An intravenous pyelogram was done which showed no excretion of dye. Because of continued oliguria he was transferred to this hospital.

Physical examination on his admission revealed enlarged, red tonsils with bilateral cervical adenopathy and moderate facial edema. The blood pressure was 94 mm. of mercury systolic and 68 diastolic.

Laboratory Data.—The urine was grossly bloody, with an occasional white blood cell and red blood cell cast in the spun sediment. The hematocrit was 29 and

16. Daly, C. A.: The Determination of Non-Protein Nitrogen with Special Reference to the Koch-McMeekin Method, J. Lab. & Clin. Med. **18**:1279, 1933.

17. Howe, P. E.: The Use of Sodium Sulfate as the Globulin Precipitant in the Determination of Proteins in the Blood, J. Biol. Chem. **49**:93, 1921.

18. Archibald, R. M.: Colorimetric Determination of Urea, J. Biol. Chem. **157**: 507, 1945.

19. Peters and Van Slyke,[13] p. 378.

20. Folin, O., and Wu, H.: A System of Blood Analysis, J. Biol. Chem. **38**:81, 1919.

21. Somogyi, M.: Nitrogenous Substances in Zinc Filtrates of Human Blood, J. Biol. Chem. **87**:339, 1930.

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24. Kern, A., and Stransky, E.: Beitrag zur kolorimetrischen Bestimmung der Harnsäure, Biochem. Ztschr. **290**:419, 1937.

25. Callow, N. H.; Callow, R. K., and Emmens, C. W.: Colorimetric Determination of Substances Containing the Grouping—CH_3CO—in Urine Extracts as an Indication of Androgen Content, Biochem. J. **32**:1312, 1938.

26. Talbot, N. B.; Berman, R. A., and MacLachlan, E. A.: Elimination of Errors in the Colorimetric Assay of Neutral Urinary 17 Ketosteroids by Means of a Color Correction Equation, J. Biol. Chem. **143**:211, 1942.

27. ACTH used in these studies was supplied through the generosity of Dr. John R. Mote, of The Armour Laboratories, Chicago.

the blood urea nitrogen 157 mg. per hundred milliliters. The sedimentation rate was 30 mm. in one hour (corrected) and the white blood cell count 22,000 per cubic millimeter.

Course in Hospital.—The patient was given penicillin, 400,000 units daily, and on the second hospital day ACTH therapy was begun, 20 mg. every six hours for five days. The oliguria persisted for four days, following which the volume of urine gradually increased, reaching 2,100 ml. on the fourteenth day in the hospital. There were gradual diminution of nitrogen retention and increased sense of well-being and appetite. The sedimentation rate dropped to 16 mm. (corrected) on the twenty-fifth hospital day. Urinary values slowly improved. A slight afternoon rise in temperature of 1 to 1.5 degree F. became apparent on the eighth hospital day and diminished gradually until his discharge on the thirty-seventh hospital day. On the fifteenth hospital day he was again given 20 mg. of ACTH every six hours for twenty-four hours, with a drop in circulating eosinophils from 364 to 123 per cubic millimeter.

ACTH treatment was instituted during the period of oliguria and gross hematuria. During five days of ACTH administration the total twenty-four hour volume of urine progressively increased from 25 to 1,250 ml. on the last day of

TABLE 2.—*Adrenal Hormone Therapy in Acute Glomerular Nephritis*

Patient	Age, Yr.	Sex	Duration of Disease	Type of Therapy	Duration of Therapy, Days	Total Dosage, Gm.	Response
D. W.	8	M	8 days	ACTH	5	0.48	1+*
R. B.	18	F	1 wk.	ACTH	12	1.20	1+*
R. K.	49	M	7 wk.	ACTH	13	1.15	1+*
				ACTH	12	0.48	1+
				ACTH	5	0.40	0
W. L.	9	M	10 days	ACTH	5	0.18	±

* Temporary increase in hematuria on cessation of therapy.

ACTH therapy. Gross hematuria persisted throughout. The blood pressure showed little change, and weight was maintained throughout this period. Blood urea nitrogen remained at a high level, i. e., 140 to 155 mg. per hundred milliliters.

After the withdrawal of ACTH, urine volume progressively increased, attaining a maximum of 2,700 ml. eight days following the last dose of ACTH. The patient lost 2 Kg. in weight during this period. For one day after withdrawal of ACTH, a marked sodium and chloride diuresis occurred, amounting to 140 and 120 milliequivalents, respectively, with the patient on a low sodium chloride diet. Blood urea nitrogen fell to a normal level, and the urine sediment improved considerably. However, microscopic hematuria persisted throughout the period of hospitalization (thirty-seven days). Three weeks after his discharge an Addis count showed slight but definite improvement in hematuria. Proteinuria was unchanged during the period of treatment but fell rapidly during the ten days after ACTH administration was discontinued.

Comment.—There was no evidence of reversible change in the patient's course during ACTH treatment other than the progressive improvement in urine volume. Persistent positive cultures for hemolytic streptococcus necessitated penicillin treatment from the second to the nineteenth day of disease. Three months later a follow-up study showed no proteinuria, only rare red blood cells in the spun urine sediment and no other evidence of disease.

Case 2.—Three weeks prior to her admission to the hospital R. B., a 19 year old woman, had coryza with slight sore throat. Her condition improved during the next week. Nine days before her admission she experienced a tight sensation in her abdomen without nausea or vomiting. Five days prior to admission she noticed swelling of the legs and ankles and dark, cloudy urine. Her physician diagnosed acute glomerulonephritis and advised rest in bed and a low salt diet. Her eyes became puffy, and on the morning of admission she had a nosebleed.

Results of Physical Examination.—The blood pressure was 160 mm. of mercury systolic and 90 diastolic. Her heart was enlarged to the left with a diastolic gallop and a systolic murmur. The mitral first sound was accentuated. The liver extended 1½ fingerbreadths below the right costal margin. There were pitting edema of the ankles (1 +) and slight facial edema.

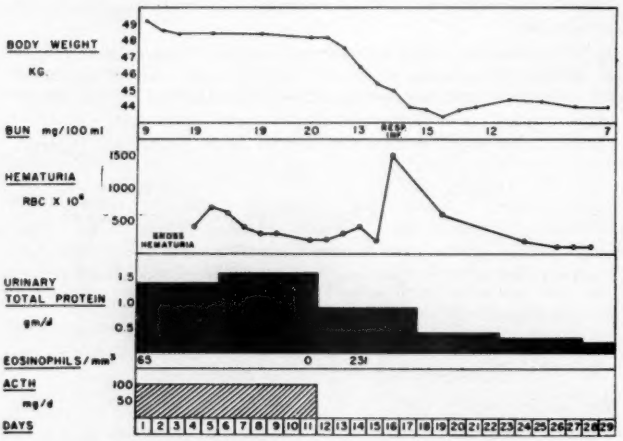

Chart 1 (patient R. B.).—Results of use of ACTH in acute nephritis.

Laboratory Findings.—The urine was concentrated to a specific gravity of 1.031, with 1 + reaction for protein and an Addis count of 400,000,000 red blood cells, 60,000,000 white blood cells and 5,000,000 casts per twenty-four hours. The hemoglobin concentration was 12.4 Gm., the sedimentation rate 23 mm. per hour and the phenolsulfonphthalein excretion 66 per cent in two hours. A nose and throat culture grew Streptococcus hemolyticus; blood urea nitrogen was 19 mg. per hundred milliliters; the carbon dioxide–combining power was 23.5 millimoles per liter. Serum chlorides were 112 milliequivalents per liter; serum total protein was 6.2 Gm., fasting blood sugar 69 mg. and serum uric acid 4.9 mg. per hundred milliliters.

Course in the Hospital.—Twenty-four hours after her admission she was given ACTH, 100 mg. daily (25 mg. every six hours) for the subsequent twelve days. The important changes are summarized in chart 1. Penicillin was administered during the first twelve days of hospitalization. On the twenty-second day of hospitalization the patient had an infection of the upper respiratory tract with aggravation of the nephritis. Three days later typical chickenpox appeared.

Microscopic hematuria and proteinuria did not disappear until the eleventh day of her disease. The sedimentation rate on her admission was 23 mm. On the seventh hospital day it had fallen to 7 mm. and remained between 4 and 5 mm. for the next seven days. On the eighteenth hospital day it had risen to 20 mm., where it remained during the course of her chickenpox, falling to 12 mm. shortly before her discharge on the fifty-first hospital day.

Comment.—Gross hematuria disappeared forty-eight hours after ACTH administration was begun. However, there was no further improvement in hematuria or proteinuria during the subsequent ten days of therapy. After the withdrawal of ACTH, a transient exacerbation of the hematuria occurred which may have been coincidental but which has been observed in other patients. Six weeks after her discharge, the hematuria had almost disappeared and the urine was protein free.

CASE 3.—*First Admission.*—R. K., a man 49 years of age, entered the hospital with a six weeks' history of gross hematuria and swelling of ankles and feet. One week previously a sudden generalized exfoliative dermatitis had developed. He had had psoriasis for twenty-four years, with progressive arthritic changes over the past three years and daily temperature elevation to 100 or 100.5 F. (oral) for ten years.

Physical examination revealed an oral temperature of 100.5 F. and blood pressure of 170 mm. of mercury systolic and 86 diastolic, with generalized severe acute exfoliative dermatitis. There were also signs of rheumatoid arthritis, pitting edema of the lower part of both legs and feet and periorbital edema.

Laboratory studies revealed a hematocrit of 33 per cent and a white blood cell count of 12,000 per cubic millimeter. The corrected sedimentation rate was 30 mm. in one hour. The urine was mahogany colored. The p_H was 6.5 and the specific gravity 1.008, and there was proteinuria (4+). The spun sediment showed 25 to 30 red blood cells, 1 to 2 white blood cells and an occasional hyaline and granular cast per high power field. The blood urea nitrogen was 8 mg. per hundred milliliters. Phenolsulfonphthalein excretion was 15 per cent in fifteen minutes and 25 per cent in two hours. The serum protein was 5.5 Gm. per hundred milliliters (2.3 Gm. of albumin and 3.2 Gm. of globulin).

Hospital Course: The patient was placed on a diet of low salt content, 50 Gm. of protein and constant fluid intake of 1,500 ml. per twenty-four hours. ACTH treatment (25 mg. every six hours by intramuscular injection) was instituted (chart 2). Within twenty-four to forty-eight hours there was pronounced improvement in the manifestation of exfoliative dermatitis; joint motion was increased, and within three days the scaling and gross hematuria had disappeared. The patient received seventeen days of ACTH therapy, with gradual increase in blood urea nitrogen and slight reduction in the number of red blood cells per high power field but no change in proteinuria. During ACTH therapy the corrected sedimentation rate dropped from 30 mm. per hour to 7 mm., but rose again to 28 mm. within one week of the cessation of therapy. The serum total protein remained constant at 5.5 Gm. per hundred milliliters.

Second Admission—Since his discharge from the hospital one month previously there had been a mild return of the exfoliative dermatitis. The urine during that time continued to show blood, albumin and rare casts, microscopically. His blood pressure remained elevated. He entered the hospital this time for a second course of ACTH treatment.

Physical examination revealed a blood pressure of 180 systolic and 100 diastolic and evidence of return of activity in skin lesions.

Laboratory studies showed 20 to 30 red blood cells and a rare cast per high power field examination of spun urine sediment. The hematocrit was 37 and the corrected sedimentation rate 32 mm. per hour. The phenolsulfonphthalein excretion was 5 per cent in fifteen minutes and 30 per cent in two hours. The blood urea nitrogen was 11 mg. and serum protein 5.5 Gm. per hundred milliliters (albumin 3.4 Gm. and globulin 2.1 Gm.).

Hospital Course: A second course of treatment with ACTH, 10 mg. every six hours, was given for eleven days. The skin once again cleared rapidly. There was a slight reduction in the urinary red blood cells and white blood cells per twenty-four hours as determined by Addis count. The blood urea nitrogen rose from 11 mg. per hundred milliliters to 22 mg. The sedimentation rate remained unchanged (32 mm. per hour, corrected).

Third Admission.—The patient was admitted to the hospital for a third time two months after his discharge. He had taken 40 mg. of ACTH and 25 mg. of

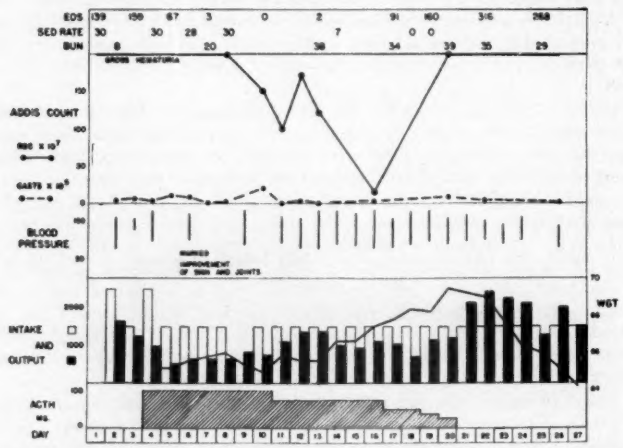

Chart 2 (patient R. K.).—Results of use of ACTH in patient with psoriasis, arthritis and nephritis.

testosterone propionate daily while at home. Because of a gain in weight of 10 Kg. and development of headaches, edema and vomiting, ACTH therapy was stopped with a concurrent diuresis. Thereafter, however, his dermatitis gradually became worse. Six weeks before his admission he again began taking ACTH, 40 mg. per day, without clinical improvement. After seven days of this therapy, the dose was increased to 80 mg. a day, with temporary improvement in the dermatitis but with concurrent edema, necessitating the use of mercurial diuretics and reduction of the dose of ACTH from 80 to 25 mg. per day. Ten days before his admission cortisone therapy, 90 mg. a day, was instituted, but the dermatitis became worse. The patient was readmitted with severe exfoliative dermatitis, fever, malaise and tachycardia.

Results of Physical Examination: The temperature was 99.2 F. (oral), the pulse rate 112 and the blood pressure 174 systolic and 68 diastolic. Severe diffuse exfoliative dermatitis and pretibial pitting edema (2+) were present.

Laboratory Data: Urinalysis showed 2 + reaction for protein, 3 to 4 red blood cells per high power field and rare cell casts in the spun sediment. The sedimentation rate (corrected) varied between 30 and 38 mm. Fasting eosinophils numbered 452 per cubic millimeter. A four hour test with 25 mg. of ACTH showed a 65 per cent drop in circulating eosinophils.

Hospital Course: During the first three days in the hospital the rectal temperature ranged between 100.4 and 101.2 F. From the third hospital day ACTH, 80 mg. daily intramuscularly, was given for five days. There was slight improvement in the dermatitis but no essential change in the urinary findings, which on admission had shown by the semiquantitative technic (Addis) improvement over the values recorded during the last admission.

Comment.—Despite pronounced improvement in all other signs of systemic disease (arthritis, exfoliative dermatitis), the renal manifestations showed little change, with the exception of the disappearance of gross hematuria. There was, however, little further improvement in hematuria during therapy. In addition, during therapy the blood urea nitrogen rose as did the blood pressure, and edema associated with therapy necessitated use of diuretics. In a sense, this patient served as his own control, and the striking difference between the results of therapy in the psoriasis and in the concomitant nephritis is evident.

Case 4.—W. L., a boy 9 years of age, was observed to have acute tonsillitis with fever, cervical lymphadenopathy and intractable vomiting ten days prior to his admission to the hospital. Seven days before admission the blood pressure was observed to be 110 mm. of mercury systolic and 70 diastolic and urinalysis showed protein, red and white blood cells and casts in the spun sediment. Results of urinalyses had been normal two and a half years and five months before his admission. Vomiting persisted, and thirty-six hours before his admission he became anuric. He had one convulsion shortly before admission. His childhood had been complicated by whooping cough in infancy, retarded development, repeated unexplained bouts of fever and vomiting at the age of 5 years and scoliosis due to hemivertebrae with neurogenic bladder.

Physical examination revealed a well nourished, drowsy child with hypertrophied tonsils, cervical lymphadenopathy, minimal periorbital edema, pallor and moderate cardiac enlargement. The blood pressure was 115 mm. of mercury systolic and 80 diastolic. The oral temperature was 97.6 F. Neurologic examination showed only an atonic bladder.

Laboratory findings revealed a negative blood Hinton reaction, hematocrit of 31 per cent, white blood cell count of 24,000 and corrected erythrocyte sedimentation rate of 28 mm. per hour on admission. The urine had a p_H of 5.5, specific gravity of 1.003 to 1.017, 1 to 4 + reaction for protein, many red and white blood cells and occasional granular casts in the spun sediment. The urine was sterile and nose and throat cultures grew no beta hemolytic streptococci. Phenolsulfonphthalein excretion on the tenth hospital day was 50 per cent in two hours and the urea clearance (standard) 17 per cent. Blood chemical studies revealed urea nitrogen of 90 mg. per hundred milliliters, carbon dioxide-combining power of 14.9 millimoles per liter, serum chloride of 90 and serum calcium of 5.1 milliequivalents per liter, serum phosphate of 1.3 millimole per liter and serum total protein of 5.7 Gm. and fasting sugar of 124 mg. per hundred milliliters. The electrocardiogram made on admission was normal, and roentgenograms of chest and abdomen were not remarkable.

The hospital course started with a diuresis on the third day, so that he lost 5.2 Kg. in body weight by the tenth day. He had received a single dose of 20 mg. of ACTH on the second hospital day. Concomitant with the diuresis his blood

chemical values improved rapidly to normal levels. On the twenty-third hospital day, because of persistent hematuria, ACTH therapy was again started, 40 mg. daily for four days. No change was observed in phenolsulfonphthalein excretion, Addis counts or hematocrit. Acidosis and slight urea retention followed this therapy, while he was fed a diet containing 40 Gm. of protein daily. He was discharged without edema or hypertension and with proteinuria (1+).

Comment.—In this child with acute nephritis it is difficult to ascertain whether the onset of diuresis had any correlation with the single dose of 20 mg. of ACTH administered immediately before. The four day course of therapy starting on the twenty-third day in the hospital caused no change, and it is difficult to believe from these data that the natural course of the disease was modified.

Summary of Effect in Four Cases of Acute Nephritis.—Evaluation of the treatment of acute nephritis with ACTH is difficult because of the natural tendency of the disease process, particularly in young persons, to improve spontaneously. On the basis of the data presented, it is impossible to detect a causal relationship between administration of ACTH and improvement in the nephritic picture. The lack of improvement of the renal disease in contrast to the pronounced improvement of an associated psoriasis in one patient (case 3) is noteworthy. In addition, in this patient edema, hypertension and azotemia following ACTH therapy were troublesome and apparently outweighed the beneficial effects on the renal disease. It is also of interest that in case 1 proteinuria was unchanged during the period of treatment but decreased rapidly during the ten days after ACTH administration was discontinued. In case 1 there was no immediate change in gross hematuria in spite of therapy, whereas in cases 2 and 3 disappearance of gross hematuria followed ACTH administration, but little further change occurred in spite of continued administration of the hormone. In all 3 cases a temporary increase in hematuria occurred on cessation of therapy, and in case 3 the sedimentation rate, which had dropped on ACTH treatment, rose again within one week of cessation of therapy. These data suggest a temporary beneficial effect but are not conclusive.

It is possible that the known effect of ACTH in decreasing the inflammatory response may have some long term benefit in decreasing the amount of glomerular damage caused by fibrosis secondary to this inflammatory response. Such a possibility, however, cannot be substantiated from the data presented here, and because of the natural course of the disease must await long term study of a large number of such cases.

II. SUBACUTE AND CHRONIC GLOMERULAR NEPHRITIS

Seven patients with subacute or chronic nephritis have been treated with ACTH or cortisone [28] (table 3).

28. Cortisone for this study was purchased from allocations by the Committee for the Investigation of Cortisone of the National Academy of Sciences.

CASE 1.— P. O'B., a 14 year old school boy, was treated with ACTH (40 to 80 mg. daily). Three years before the first admission he had had hematuria, and a diagnosis of glomerulonephritis was made. In January 1949 he was admitted for gross hematuria following beta hemolytic streptococcus pharyngitis. He was given penicillin treatment and roentgen therapy to the pharynx, with gradual improvement in the urinary findings. The phenolsulfonphthalein excretion was 25 per cent in fifteen minutes and 75 per cent in two hours.

His second admission in April 1949 showed no change in the results of physical examination. Examination of the urine revealed a 2 to 3+ reaction for protein, with 2 to 20 red blood cells visible microscopically in the spun sediment. On the seventh hospital day he was given three days of ACTH therapy (40 mg. daily). There was definite clearing of the microscopic hematuria, with recurrence following cessation of therapy. On the thirty-second hospital day he was again given four days of ACTH therapy (40 mg. daily). Again, the microscopic hematuria appeared to clear, with an increase following cessation of therapy.

TABLE 3.—*Adrenal Hormone Therapy in Subacute and Chronic Glomerular Nephritis*

Patient	Age, Yr.	Sex	Duration of Disease	Type of Therapy	Duration of Therapy, Days	Total Dosage, Gm.	Response
P. O'B.....	14	M	4 yr.	ACTH	23	0.120	2+
					24	0.160	2+
					28	2.20	1+
T. O'T.....	36	M	6 yr.	ACTH	9	0.90	0*
J. Mc.....	13	M	5 mo.	ACTH	9	0.80	0
A. S.....	25	F	2 yr.	ACTH	6	0.36	0
M. DiG.....	26	M	4 mo.	Cortisone	10	1.00	0*
V. A.....	29	F	2 yr.	Cortisone	14	1.40	0*
G. H.....	16	F	4 yr.	Cortisone	14	1.40	0

* Slight increase in hematuria on cessation of therapy.

On the third admission in December 1949 the patient again had a noticeable increase in hematuria following beta hemolytic streptococcus pharyngitis. He was treated with penicillin, and from the twelfth hospital day ACTH (80 mg. per day) was administered for twenty-eight days in conjunction with penicillin (2,000,000 units per day) and chloramphenicol (chloromycetin®; 3 Gm. per day). There was a gradual diminution in the formed elements in the urine, with one exacerbation of gross hematuria following the development of otitis media on the fourteenth hospital day. Skin tests for sensitivity to the beta hemolytic streptococcus gave positive reactions prior to ACTH therapy and showed a definite diminution in response during the treatment period. The patient was discharged on the forty-fifth day from the hospital with pronounced decrease in hematuria.

Comment.—This patient was unusual in that during the second admission the appearance and disappearance of hematuria appeared to be correlated with ACTH therapy. There was, however, no correlation on the third admission.

CASE 2.—T. O'T., a 32 year old man, was treated with ACTH, 100 mg. daily, for nine days. His urine was first noted to contain red and white blood cells and casts four years before his admission to this hospital. The past history was pertinent in that he had had scarlet fever one year prior to this discovery. Since that time frequent examinations had disclosed persistent hematuria, proteinuria and cylindruria. There had been no evidence of hypertension or of nitrogen retention. Hemo-

globin values had been 10 to 11 Gm. per hundred milliliters. Beta hemolytic streptococci had been cultured from the throat on several occasions, but the administration of penicillin had failed to affect the urinary findings.

Results of physical examination were completely normal. The blood pressure was 120 mm. of mercury systolic and 80 diastolic. There was no evidence of edema.

Laboratory data showed a hemoglobin concentration of 11 Gm. The corrected sedimentation rate was 15 mm. in one hour. The urine was clear and the p_H 5.0, with 2 to 3+ reaction for protein. The spun sediment was loaded with red blood cells and contained 2 to 5 white cells and occasional granular casts per high power field. Urea clearance was 17 per cent of normal (standard clearance), and the phenolsulfonphthalein excretion was 40 per cent in two hours. Blood urea nitrogen was 24 mg., and serum uric acid was 11.6 mg. per hundred milliliters. Serum protein was 5.7 Gm. per hundred milliliters, with 3.5 Gm. of albumin and 2.2 Gm. of globulin.

Hospital Course.—The patient was placed on a low purine, low salt diet, containing 40 Gm. of protein. Fluids were restricted to 1,500 ml. per day. On the sixth hospital day he was given ACTH, 25 mg. four times daily by intramuscular injection for nine days. There was no change in the urinary sediment, proteinuria or subjective state during the period of therapy, nor was there change in the serum proteins or fractions thereof as measured by the Tiselius pattern. However, the patient lost 7 pounds (3.2 Kg.) of body weight, and his blood urea nitrogen rose to 73 mg. per hundred milliliters. Reactions to the skin tests for sensitivity to the beta hemolytic streptococcus were decidedly positive before ACTH therapy and became negative during treatment. Following cessation of ACTH treatment, there was a definite increase in hematuria which persisted for fourteen days. He was discharged on the eighteenth hospital day, and, when he was seen one week later, on an ad libitum fluid intake the blood urea nitrogen had fallen to 21 mg. per hundred milliliters. There was no change in the urinary findings or the patient's clinical status.

Comment.—In this patient weight loss and increased blood urea nitrogen were probably due to fluid restriction during the ACTH therapy, as well as the effect of the hormone itself on protein metabolism. It is of interest that again a definite increase in hematuria followed cessation of therapy.

Case 3.—J. M., a 13 year old boy, was treated with ACTH, 100 mg. daily, for eight days. Three months before his first admission to this hospital he showed swelling of the face, hematuria and dyspnea. Mild hypertension, cylindruria and nitrogen retention were observed at that time. After two months of rest in bed at home, the edema and dark-colored urine had disappeared, but the proteinuria and hematuria persisted. Because of failure of hematuria and proteinuria to clear on continued rest in bed, he was admitted for a second time.

Results of physical examination were normal except for a blood pressure of 140 mm. of mercury systolic and 80 diastolic.

Laboratory data showed a hematocrit of 37 per cent and a white blood cell count of 9,400. The corrected sedimentation rate was 30 mm. in one hour. The urine was slightly cloudy, with a p_H of 5.0, and a 4+ reaction for protein. The spun sediment showed 5 to 7 red blood cells, 4 to 6 white cells and frequent fine and coarse granular casts per high power field. The urea clearance was 68 per cent of normal, and the phenolsulfonphthalein excretion was 5 per cent in fifteen minutes and 50 per cent in two hours. Blood urea nitrogen was 11 mg. per hundred milliliters. The serum protein was 6.2 Gm. (2.1 Gm. of albumin, 4.1 Gm. of globulin).

Hospital Course.—The patient was placed on a constant diet containing 200 mg. of sodium and 45 Gm. of protein. After seven days ACTH therapy was started, 25 mg. every six hours, by intramuscular injection. There was some reduction in the number of red blood cells and casts as determined by Addis count but no improvement in the degree of proteinuria (chart 3). After receiving 700 mg. of ACTH, the patient showed gross hematuria, and further ACTH administration was discontinued. A daily afternoon temperature elevation of 1 degree F. was not affected by therapy with ACTH.

Comment.—This patient showed slight change in the urinary sediment on ACTH therapy but had gross hematuria during the period of treatment. No effect was seen on a slight daily temperature elevation.

CASE 4.—A. S., a woman aged 25, was treated with ACTH, 25 to 80 mg. daily, for six days. Ten months prior to her admission to the Peter Bent Brigham Hos-

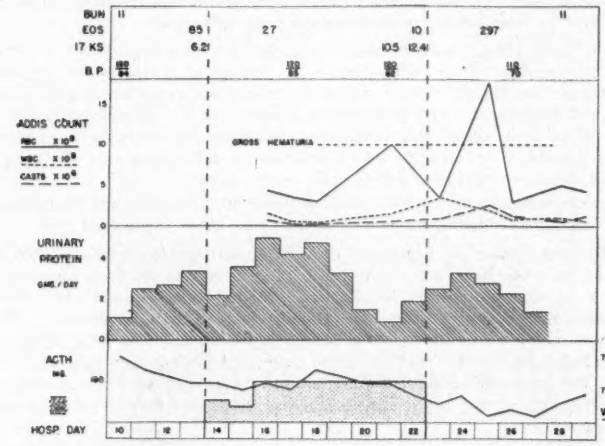

Chart 3 (patient J. M.).—Results of use of ACTH in child with subacute glomerular nephritis.

pital, and six weeks after delivery of her second child, this patient observed the onset of fatigue and generalized edema which were accompanied with proteinuria (4+), scant microscopic hematuria, hyaline casts and hypoalbuminemia. Tonsillectomy and irradiation of the posterior pharynx were not accompanied with any clinical or chemical change, other than the disappearance of generalized edema.

Physical examination at the time ACTH therapy was instituted showed nothing remarkable. The blood pressure was 120 mm. of mercury systolic and 80 diastolic; the pulse rate was 80 and the temperature 98.8 F. There was no edema.

Laboratory Findings.—The urine contained 2.7 to 4.9 Gm. of protein daily and showed a specific gravity of 1.015. No casts or red blood cells were noted. The hematocrit was 45 per cent. The blood Hinton reaction was negative. Blood urea nitrogen was 8 mg. and serum cholesterol 348 mg. per hundred milliliters.

Throat culture revealed occasional beta hemolytic streptococci. Total serum protein was 4.9 Gm. per hundred milliliters, with 3.5 Gm. of albumin.

The hospital course was afebrile and uneventful. Three hundred thousand units of procaine penicillin G for aqueous injection (crysticillin®) was administered intramuscularly daily, and 25 to 80 mg. of ACTH was given per day for six days without significant change in the excretion of urinary protein. The patient lost 1 Kg. of body weight during the treatment period.

On subsequent hospitalizations three and six months later, the patient continued to have proteinuria (1 to 3+), retained normal ability to concentrate the urine and showed normal phenolsulfonphthalein excretion, normal electrocardiograms and roentgenograms of the heart, no edema or hypertension, no anemia or remarkable microscopic hematuria. Throat cultures were free of beta hemolytic streptococci. Addis counts showed an increased number of casts. She has been continued on a 50 Gm. protein diet.

Comment.—ACTH therapy produced little change in the clinical situation of this patient as indicated by the results of the tests performed.

CASE 5.—H. DiG., a man 26 years of age, was treated with cortisone, 100 mg. daily, for ten days. Four months before his present admission to the hospital, following an infection of the upper respiratory tract he had cloudy urine, generalized edema and albuminuria. Rest in bed and a low salt and low protein diet caused a slight reduction in edema and hematuria. Reactions for albuminuria remained between 3 and 4+. A fortnight before his admission, following a mild sore throat, puffiness of his eyes developed and he noted smoky urine.

Physical examination revealed a blood pressure of 142 systolic and 80 diastolic. There was slight periorbital edema with edema (2+) of the sacrum and lower legs.

Laboratory Data.—The hematocrit was 39, the corrected sedimentation rate 30 mm. and the white blood cell count 13,600. The urine was smoky in appearance with a p_H of 6.5, a 4+ reaction for albumin, 3 to 5 red blood cells and 1 to 2 white blood cells, with numerous hyaline and granular casts in the spun sediment. The blood urea nitrogen was 13 mg,. total protein in the serum 3.2 Gm. (albumin 2.0 Gm. and globulin 1.2 Gm.) and the serum cholesterol 595 mg., per hundred milliliters. The phenolsulfonphthalein excretion was 20 per cent after fifteen minutes and 55 per cent in two hours. An intravenous pyelogram showed poor function bilaterally.

Hospital Course.—He was placed on a low salt diet containing 40 Gm. of protein. The albuminuria continued at 3 to 4+, and the urine showed 6 to 8 red blood cells per high power field. He was started on cortisone therapy, 25 mg. every six hours. This was continued for a period of ten days, during which time the number of red blood cells excreted per twenty-four hours showed no change but the number of casts excreted per twenty-four hours as determined by Addis count was reduced. Seven consecutive observations in the post-treatment period averaged 188×10^5 casts per twenty-four hours, while during a seven day period of cortisone treatment the average was 91×10^5 casts per twenty-four hours. During therapy the urine volume did not change significantly. Total urine protein excreted per twenty-four hours remained elevated. After a total dosage of 1.0 Gm. of cortisone, the patient had pain in the left flank and gross hematuria. Further therapy was discontinued.

Comment.—In this patient cortisone apparently caused a diminution in the number of casts excreted per twenty-four hours with little other change.

CASE 6.—V. A., a woman 29 years of age, was treated with cortisone, 100 mg. daily, for fourteen days. Over a period of two years she had had episodes of

transient facial edema. Within the last year she had noted edema of the ankles as well and became easily fatigued. Ten months before her admission she was found to have proteinuria (4+). She was treated by diet and rest in bed, with frequent recurrences of facial and dependent edema. Her history revealed extreme susceptibility to infections of the upper respiratory tract during the past ten years. Tonsillectomy and electrocoagulation of lymphoid tissue during this period did not change the clinical course. There was no history of hypertension.

Results of Physical Examination.—The blood pressure was 150 systolic and 94 diastolic; the temperature was 99 F., respirations 20 and pulse rate 100. The patient showed slight puffiness about the eyes and sacral edema (1+). The fundi showed a slight arteriovenous nicking and some arterial spasm.

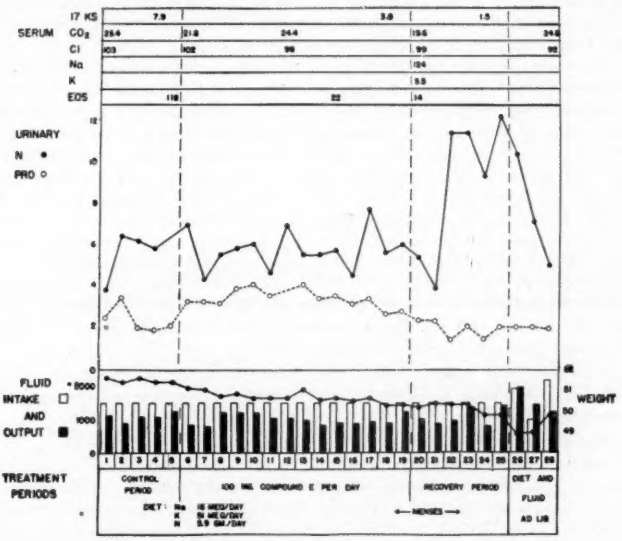

Chart 4 (patient V. A.).—Results of use of cortisone (compound E) in patient with chronic glomerular nephritis in nephrotic stage.

Laboratory Data.—The urine had a p_H of 5.5, a specific gravity of 1.022, a 3+ reaction for protein and no trace of sugar. It contained rare red blood cells, white blood cells and occasional granular casts in the spun sediment. Hematocrit was 42 per cent, the hemoglobin concentration 14.1 Gm., the sedimentation rate 37 mm. per hour and the white blood cell count 7,800. Blood urea nitrogen measured 7 mg., nonprotein nitrogen 29 mg., total protein 5.7 Gm. and albumin 3.4 Gm., per hundred milliliters. The carbon dioxide-combining power was 25.4 millimoles, chloride 103 milliequivalents and calcium 4.8 milliequivalents, per liter. Phenolsulfonphthalein excretion was 30 per cent in fifteen minutes and 55 per cent in two hours.

Hospital Course.—The patient was placed on a constant diet and fluid intake which contained 16 milliequivalents of sodium, 56 milliequivalents of potassium,

6.1 Gm. of nitrogen and a total of 1,500 ml. in fluids per day. After a suitable control period, administration of cortisone, 100 mg. daily, was begun. Addis counts and urinary protein, uitrogen, sodium and potassium excretion were followed at frequent intervals. During the treatment period there was a gradual weight loss of approximately 0.8 Kg., though the urine volume was slightly decreased as compared with the control period. Urinary protein excretion rose initially but fell to control levels, while sodium excretion was slightly diminished. Nitrogen and potassium excretion was essentially constant (chart 4).

In the period after cessation of cortisone therapy a large increase in sodium, potassium and nitrogen excretion and a small increase in chloride excretion occurred. Urinary protein continued essentially the same. The Addis counts showed only small variations in amounts of formed elements. Serum total protein, albumin and Tiselius patterns were unchanged after treatment. The sedimentation rate remained at 17 mm. per hour. After therapy, the patient was discharged from the hospital on a diet containing 50 Gm. of protein and 3 Gm. of salt.

Follow-Up Observations.—Aside from one instance of cystitis two months before readmission, which was controlled by administration of chloramphenicol, the patient had been relatively asymptomatic. Weight had fluctuated about 2 pounds (0.9 Kg.) with occasional slight pitting edema of the ankles. Dietary intake consisted of 40 to 50 Gm. of protein with moderate to low salt content. Fatigability and occasional headaches were the most prominent symptoms, and she had led a relatively inactive life in the interim. She entered the hospital five months after the previous admission for check-up. Physical examination at the time showed no essential change. The blood pressure was 130 systolic and 72 diastolic. Addis counts showed 3,000,000 to 8,000,000 red blood cells and 300,000 to 500,000 casts, with no change despite exercise. Urinary sodium excretion was increased over previous figures to 53 to 73 milliequivalents per day. Blood chemical values were essentially normal. Phenolsulfonphthalein excretion was 75 per cent in two hours and urinary total protein was 3.4 Gm. per day.

Comment.—This patient showed essentially no change in the pattern of her renal disease exclusive of electrolyte shifts produced temporarily following withdrawal of cortisone.

Case 7.—G. H., a girl 16 years of age, was treated with cortisone, 100 mg. daily, for fourteen days. Four years prior to her admission hematuria was observed following a middle ear infection complicated by cervical adenitis. Fifteen months before her admission she had cervical adenitis which responded readily to penicillin treatment. However, one week later she noted the appearance of periorbital edema. Her physician found proteinuria (4 +) accompanied with an elevation of blood pressure. The edema disappeared, but her symptoms and abnormal urinary findings persisted. She was admitted to the Peter Bent Brigham Hospital on March 19, 1949 for study and treatment.

Physical examination revealed a pale girl without visible edema. The blood pressure was 118 mm. of mercury systolic and 68 diastolic; her temperature was 100.4 F. (rectum), pulse rate 88 and respirations 24. There was persistent lymphoid hyperplasia in the posterior pharynx. Otherwise results of physical examination were not remarkable.

Laboratory Data.—Urinalysis showed a specific gravity of 1.004 to 1.019, a 0 to 3 + reaction for protein, 0 to 30 red blood cells, 50 white blood cells and occasional casts per high power field. Hematocrit was 30 to 34 and the sedimentation rate 16 to 25 mm. Total serum protein was 3.2 to 4.2 Gm. per hundred milliliters, with 2.3 to 2.6 Gm. of albumin. Phenolsulfonphthalein excretion was 5 per cent in one-half hour with a total of 40 per cent in two hours.

Hospital Course.—The patient was asymptomatic and afebrile during the thirty-seven days of hospitalization. She received 100 mg. of vitamin C daily. On the fifth hospital day she was given a constant fluid intake of 2,000 ml. and a constant diet which contained 20 milliequivalents of sodium, 72 milliequivalents of potassium and 5.4 Gm. of nitrogen per day. On the eleventh day 100 mg. of cortisone was given for the subsequent fourteen days.

During the course of therapy with cortisone a minimal drop in sodium and chloride excretion and a slight rise in potassium excretion took place. Following cessation of therapy, there were a slight increase in sodium and chloride excretion over control periods and a further rise in potassium excretion. The weight did not change. A moderate drop in total serum protein was noted during the first week of cortisone administration, but there was no significant drop thereafter. However, the daily total protein excretion increased slightly following cessation of therapy. The urinary sediment as measured by the Addis count showed no significant change.

There was no essential change in the total serum protein or the albumin to globulin ratio, nor was there any significant change in the Tiselius pattern. The sedimentation rate rose from 25 to 38 mm. during therapy and dropped to 21 mm. again on cessation. The serum levels of sodium, potassium, chloride, carbon dioxide, blood urea nitrogen or phosphate showed no important change. There was a slight fall in serum cholesterol, but it was not quantitatively significant. In general the electrolyte excretion varied as one might expect, but the course of renal disease in general was unaffected.

Comment.—This patient showed little change in the pattern of her renal disease, other than the transient changes in sodium and potassium excretion following cessation of therapy.

Summary of Effect of ACTH and Cortisone on Subacute and Chronic Glomerulonephritis.—The administration of ACTH and cortisone in 7 patients with subacute and chronic glomerulonephritis effected little change in the clinical manifestations of their renal disease or the chemical indications studied. Hematuria in one patient (case 1) decreased on administration of ACTH on two occasions, but the response was not significant on a third occasion. One (case 2) showed increased hematuria following cessation of therapy, and another (case 5) on cortisone therapy showed a definite diminution in the number of casts excreted. In general, however, there were no definite changes in the serum proteins, cholesterol or sedimentation rate, in spite of adequate evidence of adrenal stimulation in patients given ACTH and a high level of urinary 11-oxysteroids in the cortisone-treated patient. The response of the proteinuria and the excretion of formed elements were inconsistent and clinically of little significance in most cases. In addition, one patient (case 3) showed gross hematuria during the administration of ACTH. It is our opinion that there is no conclusive evidence that the administration of either ACTH or cortisone favorably affects the course of subacute or chronic nephritis.

III. NEPHROTIC SYNDROME

Six patients in the nephrotic stage of chronic glomerular nephritis have been treated with ACTH or cortisone (table 4).

CASE 1.—M. A., a man 39 years of age, entered the hospital on Nov. 7, 1949 with a four weeks' history of increasing puffiness of the face, edema, mild fatigue and constant dull headache. Soon after onset of edema the patient was noted to have a 4 + reaction for albumin, red blood cells and casts in his urine. The blood pressure varied between 130 and 120 mm. of mercury systolic. At this time he was placed on a low salt and protein diet, but in the absence of nitrogen retention the protein restriction was later removed. Lack of improvement in urinary findings and an increase in edema occasioned hospital entry for further study.

Past history revealed no antecedent infection. One brother had had nephritis at the age of 17.

Results of Physical Examination.—The blood pressure was 122 mm. of mercury systolic and 78 diastolic; the pulse rate was 78 and the temperature 98.6 F. The

TABLE 4.—*Adrenal Hormone Therapy in Nephrotic Syndrome*

Patient	Age, Yr.	Sex	Duration of Disease	Type of Therapy	Duration of Therapy, Days	Total Dosage, Gm.	Diuretic Response Following Withdrawal
M. A.	39	M	6 wk.	Cortisone	8	1.20	1+
A. J.	36	M	1 yr.	Cortisone	3	0.80	0
J. P.	15	M	2 yr.	ACTH	7	0.70	4+
				ACTH	7	0.48	4+*
G. D.	18	M	2 yr.	ACTH	7	0.70	4+
R. G.	14	M	5 mo.	ACTH	7	0.56	4+
				ACTH	5	0.40	3+
				ACTH	15	1.24	4+*
L. T.	17	M	6 wk.	ACTH	21	2.8	3+

* Diuresis initiated during therapy.

patient was pale and showed slight facial and (1 +) ankle edema. The eyegrounds were normal; cardiac measurements were at the upper limit of normal; the abdomen was full but without evidence of ascites.

Laboratory Data.—Urinary p_H was 6 and specific gravity 1.022. A 4 + protein reaction, 2 red blood cells and 1 to 2 white blood cells were present, with occasional granular casts. Hematocrit was 39 and the white blood cell count 5,800. Blood urea nitrogen measured 32 mg., serum total protein 3.2 Gm., albumin 1.5 Gm. and cholesterol 430 mg., per hundred milliliters. The carbon dioxide-combining capacity was 27.6, chloride 91, calcium 4.3, sodium 128 and potassium 4.0, milliequivalents per liter. Phosphorus was 1.5 millimoles per liter. The electrocardiogram showed first degree heart block.

Hospital Course.—The patient was placed on a constant diet and fluid intake composed of 1,800 calories, 285 Gm. of carbohydrate, 36 Gm. of protein and 61 Gm. of fat per day. After a control period, he was given a chloride load in the form of ammonium chloride, 8.5 Gm. the first day and 10.5 Gm. the second day, to which he responded on the third day with a diuresis of 1,000 ml. and consequent rise in serum chloride from 90 to 106 milliequivalents per liter. Further chloride administration produced no further diuresis. Subsequently he was given a potassium load and a mercurial diuretic without any diuresis. This was followed with a load

of 7.5 Gm. of sodium bicarbonate and 7.2 Gm. of potassium citrate separately without appreciable change in weight, urine volume or blood chemical values. Cortisone therapy was then started. Initially 200 mg. per day was given for four days; then the amount was decreased to 100 mg. each day for four additional days. Prior to cortisone administration a four hour ACTH test (25 mg.) showed a 74 per cent drop in eosinophils. During cortisone therapy and four days after its conclusion, use of ACTH caused no fall in eosinophils.

However, twelve days after therapy ended a 73 per cent fall was noted. A sodium load administered as bicarbonate on two occasions during cortisone therapy was without significant effect on blood chemical levels. There was a moderate fluid retention each time ACTH was administered, but toward the end of therapy the output increased and the patient lost a small amount of weight. Edema became more dependent in character but did not decrease in extent. Addis counts and twenty-four hour urinary protein values were unchanged throughout the hospital course. Reactions to skin tests for sensitivity to the beta hemolytic streptococcus were markedly positive before cortisone therapy and diminished during treatment. On cessation of therapy, there was no definite increase in urine volume, electrolyte excretion or weight loss. The period of cortisone therapy was accompanied with a decided increase in potassium excretion and a negative potassium balance. This was reflected in a moderate increase in serum carbon dioxide-combining power and a decrease in serum chlorides (hypochloremic alkalosis) which reverted after cessation of therapy. There was also a definite decrease in the total exchangeable body potassium as measured by the radioactive isotopic (K^{42}) dilution technic.[29]

Comment.—In this patient the administration of cortisone had little observable effect on diuresis or on the urinary and plasma chemical manifestations of the disease. This is in contrast to the diuresis and electrolyte loss which may accompany and follow ACTH administration. The usual effect of cortisone in increasing urinary excretion of potassium was observed. Of possible significance is the clinical observation that the edema became less generalized and more dependent, suggesting possibly a shift of water from cells to extracellular compartment.

Case 2.—A. J., a 36 year old man, was treated with cortisone, 200 mg. daily, for four days. One year before his admission to the hospital he noted ankle edema, and four and a half months before his admission he had become pale and gained 35 pounds (15.9 Kg.) with massive edema. Treatment with diuretics and diet had not altered his course.

Results of Physical Examination.—The blood pressure was 150 systolic and 110 diastolic; there was massive edema of the legs, scrotum, penis and abdomen. There were rales at the bases of both lungs and evidence of ascites.

Laboratory Data.—Blood urea nitrogen was 65 mg. and total protein 3.5 Gm. per hundred milliliters. Carbon dioxide-combining power was 14 millimoles per liter; serum sodium was 144 and serum potassium 5.3 milliequivalents per liter; hematocrit was 19 per cent. The urine showed protein (4+), with occasional granular casts, 4 white cells and 3 red cells per high power field.

Hospital Course.—On the fifth hospital day the patient was given cortisone, 50 mg. every six hours, for four days. During this time there was no change in the daily excretion of protein or in the excretion of red blood cells or casts as measured by the semiquantitative Addis technic. There was no change in the total serum protein level or in the general clinical status, and no diuresis occurred.

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29. Corsa, L., Jr.; Olney, J. M., Jr.; Steenburg, R. W.; Ball, M. R., and Moore, F. D.: The Measurement of Exchangeable Potassium in Man by Isotope Dilution, J. Clin. Investigation, to be published.

Because of the extreme degree of respiratory embarrassment, therapy with cortisone was discontinued, and the patient was relieved by paracentesis and concomitant intravenous therapy with salt-poor albumin.

Comment.—From this brief period of therapy no conclusions can be drawn concerning the efficacy of cortisone, but there was no change in the chemical or physical signs of the disease, nor did a diuresis ensue during or following cortisone administration (total dose, 800 mg.).

CASE 3.—J. P., a boy 15 years of age, first entered this hospital at the age of 13, on Sept. 19, 1947. Four months previously he had noted the gradual onset of generalized swelling, particularly prominent in the ankles and around the eyelids, coming on apparently one or two weeks after an infection of the upper respiratory tract.

Results of Physical Examination.—The patient was in no discomfort and showed slightly puffy eyelids and pitting edema almost up to the nipple line. The blood pressure was 108 systolic and 62 diastolic. There was definite fluid in the abdomen, and the scrotum and penis were markedly edematous.

Laboratory Data.—The urine showed protein (4+), with only occasional red blood cells, white blood cells and casts. The phenolsulfonphthalein excretion was 12, 19, 29 and 14 per cent for a total of 74 per cent in two hours. The throat cultures showed normal flora. Urea clearance was 85 per cent of normal. Serum proteins were less than 3.2 Gm., and albumin measured 0.9 Gm. per hundred milliliters. The carbon dioxide-combining power was 20.5 millimoles and serum chloride 108 milliequivalents per liter. Cholesterol was 1,165 mg. per hundred milliliters. The hematocrit on entry was 50; later the values averaged 40. Basal metabolism was —36 per cent below standard.

Hospital Course.—The patient had seven hospital admissions over the subsequent two and a half years, usually preceded by infections of the upper respiratory tract followed by pronounced generalized edema. He was usually treated with a low salt diet and intravenous injections of salt-free albumin.

Six hours before the present admission, the patient awakened with a dull pain in the back and left flank. On entry to the hospital he was found to be seriously edematous. He was given albumin intravenously for several days with an excellent diuresis. After his diuresis, however, he slowly reaccumulated fluid.

On the forty-fifth hospital day a course of ACTH treatment was begun. During this and following admissions in similar circumstances, he was treated with ACTH for a total of four different courses. These are represented in chart 5.

Course 1: The patient was on a constant diet with fluid intake varying between 1,800 and 1,300 ml. per day. He was given 100 mg. of ACTH daily in divided doses. Proteinuria decreased from an initial value of 7 to 8 Gm. to 4 to 5 Gm. per day during the last part of the ACTH period and remained between 4 and 5 Gm. per day during the recovery period. Addis counts showed little change in sediment, averaging about 2,000,000 to 3,000,000 red blood cells, 3,000,000 to 4,000,000 white blood cells and 400,000 to 600,000 casts per twenty-four hours before and after treatment. The blood urea nitrogen was never above normal levels, while the serum proteins rose from 3.2 to 3.8 Gm., with albumin rising from 1.5 to 2.2 Gm. per hundred milliliters. Serum cholesterol values were essentially unchanged during or after treatment. The sedimentation rate remained constant at 22 mm. per hour. Excretion of 17-ketosteroids rose from 4.9 to 8.8 mg. per twenty-four hours during the ACTH treatment period, and eosinophils at the beginning of therapy were 354, with a 67 per cent drop after forty-eight hours of ACTH treatment. The counts steadily fell during treatment to a low

value of 3 cells at the end of ACTH therapy and subsequently rose to 233 during the recovery period.

Course 2: The patient was treated with 100 mg. a day of ACTH for four days at a time; his weight was stabilized after a partial diuresis. His fluid intake averaged 1,100 ml. per day, and he was being treated concurrently with 50 Gm. of salt-free albumin a day, which program had been constant for thirty-five days previously. During and after treatment with ACTH the proteinuria or cellular constituents of the urine showed no change. Following withdrawal of ACTH, however, there was a sharp rise in urine volume, with concomitant edema loss. Blood urea nitrogen, total protein and sedimentation rate were all unchanged during the observation period.

Course 3: On a subsequent admission during a spontaneous diuresis after an infection of the upper respiratory tract, the patient was given 100 mg. of

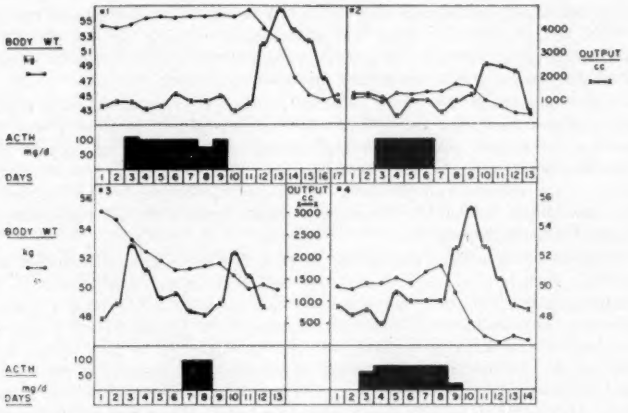

Chart 5 (patient J. P.).—Results of four courses of ACTH therapy in patient with nephrotic syndrome.

ACTH for two days. During this course of treatment his steady decline in weight was interrupted with a slight gain. Proteinuria and sediment were not changed either during or after treatment. The eosinophil count dropped from 275 to 128, for a fall of 54 per cent. Cholesterol remained at 700 to 800 mg. per hundred milliliters, and other blood and serum values showed no change.

Course 4: Later on during the same admission, after his diuresis had apparently ceased, the patient was given a course of seven days of ACTH in a dosage of 80 mg. per day. During the treatment period he gained 2.6 Kg. in weight. His face became flushed and rounded, and there was an increase in periorbital edema. The proteinuria was not altered at any time, nor was the urinary sediment changed. Blood urea nitrogen, sedimentation rate and cholesterol were not changed. Total serum protein rose from 3.7 to 3.9 Gm. per hundred milliliters. Eosinophil counts decreased from an initial count of 373 to 6 per cubic millimeter at the end of the treatment period.

After cessation of the treatment, his urine output increased greatly and his weight decreased. During this period sodium excretion was decidedly increased.

Follow-Up Observation.—After discharge he did fairly well, gradually accumulating only a moderate amount of edema fluid and then stabilizing in a fairly comfortable state on a moderate protein, low salt diet.

Comment.—This case illustrates the consistency with which the water and electrolyte diuresis can be accomplished in the nephrotic patient following withdrawal of ACTH therapy administered for as little as four days. While the urinary sediment, proteinuria and serum proteins were inconsistently affected, the loss of edema was predictable and of definite clinical benefit.

CASE 4.—G. D., a man 18 years of age, was treated with ACTH, 80 mg. daily, for five days. He was first seen at this hospital with a five weeks' history of generalized swelling, appearing concurrently with an infection of the upper respiratory tract and sore throat.

Results of Physical Examination.—The blood pressure was 110 mm. of mercury systolic and 88 diastolic; there was anasarca, including periorbital edema and minimal ascites. The pharynx was slightly injected. The remainder of the physical examination showed nothing remarkable.

Laboratory Data.—The urine contained protein (4 +), with numerous hyaline and granular casts but no red or white blood cells. Hematocrit was 46; blood urea nitrogen measured 30 mg., falling to 26 and 15 mg. Serum total protein was less than 3.2 Gm., with albumin of 0.9 Gm., and serum cholesterol was 755 mg. per hundred milliliters. Phenolsulfonphthalein excretion totaled 60 per cent in two hours. Throat culture showed normal flora. A roentgenogram revealed bilateral hydrothorax.

Hospital Course.—The patient was given a five day course of treatment with ACTH, 20 mg. four times a day. He had been losing weight prior to the administration of the drug but gained a slight amount during ACTH therapy. He had a modest diuresis following withdrawal. Later he was given albumin and ion exchange resins with considerable improvement. He returned three weeks later, at which time results of physical examination were essentially the same as on his discharge. This time he was placed on a constant diet and was given a seven day course of ACTH, 25 mg. every six hours. There was a slight gain in weight during ACTH therapy. After withdrawal of therapy, diuresis reached 5,860 ml. per day, with a weight loss of 14 Kg. over a nine day period. There was a pronounced reduction in the number of casts excreted in a twenty-four hour period, as measured by the semiquantitative Addis technic. Proteinuria also definitely decreased, more notably after cessation of ACTH therapy. An initial serum cholesterol of 575 mg. per hundred milliliters fell to 380 mg. two weeks after cessation of therapy. Serum proteins rose from less than 3.2 Gm. in the pretreatment period to 4.7 Gm. per hundred milliliters two weeks after cessation of therapy. The eosinophils on fasting were 512 per cubic millimeter five days prior to therapy and fell to 11 on the seventh day of therapy, rising again to a value of 410 seven days after cessation of therapy. Skin test reactions for sensitivity to the beta hemolytic streptococcus were positive before ACTH therapy and became negative during treatment.

Comment.—This patient showed excellent "rebound" diuresis following withdrawal of ACTH therapy, which was accompanied with slight elevation of serum total protein and decrease in cylindruria and proteinuria.

CASE 5.—R. G., a 15 year old school boy, entered the Peter Bent Brigham Hospital on Aug 12, 1949. Two weeks before his admission the patient awoke one

morning with puffy eyes. A physician was consulted, who discovered proteinuria and referred the patient to this hospital. There was no preceding or concomitant infection of the upper respiratory tract.

First Admission.—Results of Physical Examination: The blood pressure was 135 mm. of mercury systolic and 80 diastolic. By now the patient displayed conspicuous generalized edema and ascites. The heart was normal. The teeth were grossly normal. There was nothing else of note in the results of examination.

Laboratory Data: The urine showed protein (4+) and many granular casts, but no red blood cells or white blood cells. Hematocrit was 46 on admission and remained normal throughout the stay in the hospital. The blood urea nitrogen was 18 mg. per hundred milliliters on admission and later dropped to 4 mg. Serum protein was 2.9 Gm., with 0.7 Gm. of albumin. Cholesterol measured 572 mg. per hundred milliliters. Phenolsulfonphthalein excretion totaled 65 per cent in two hours. Bilateral maxillary sinusitis was demonstrated roentgenographically, but there were no abnormal organisms on throat culture. On a low salt, low protein diet the patient had a diuresis of 13 Kg., and the degree of proteinuria greatly diminished.

Further Course: The patient did well for several months, until an infection of the upper respiratory tract developed which led to generalized swelling, anorexia, abdominal pain and vomiting. This time the patient entered the hospital with edema and hemoconcentration. He was treated with penicillin and fluids intravenously and a Miller-Abbott tube was inserted. On this regimen he improved slowly. The opinion was that he had bacterial peritonitis. The patient was discharged home much improved and almost free of edema on Dec. 9, 1949.

Subsequently, another respiratory infection developed one week after his discharge and was treated with penicillin. During the two months prior to his second admission he accumulated 7 Kg. of edema and experienced nausea and vomiting on occasions.

Second Admission.—Results of Physical Examination: The blood pressure was 120 mm. of mercury systolic and 80 diastolic. There were massive edema of the legs, moderate ascites and respiratory wheezes throughout the chest.

Laboratory Data: The urine showed protein (4+), with many hyaline and granular casts, occasional red blood cells and 1 to 10 white blood cells per high power field.

Hospital Course: The patient was placed on a high fat, 50 Gm. protein, low salt diet with constant fluids; ACTH, 20 mg. intramuscularly, was given every six hours. On this and two successive occasions there was a profuse loss of edema fluid, with a total weight loss of 11 Kg. on his discharge from the hospital on the seventy-sixth day.

During the first seven day period of administration of ACTH there was appreciable fluid retention with a gain in weight of 3.2 Kg. The Addis count showed slight improvement, particularly in the number of casts excreted. The serum cholesterol, which was 1,112 mg. per hundred milliliters, showed no change in the seven day period. The 17-ketosteroid excretion rose from 3.8 to 8.8 mg. during the period of ACTH administration, and the circulating eosinophils fell from 446 to 17 on the third day of ACTH.

On the withdrawal of ACTH, beta-hypophamine (pitressin®), 2 units every three hours, was administered intramuscularly for six days in an attempt to study the influence of the posterior portion of the pituitary on the "rebound" diuresis. During the first three days of administration of beta-hypophamine, urine volume remained at 700, 900 and 1,000 ml. per day, the sodium excretion rose from 0.95 milliequivalents to 14 and chloride excretion from 27 milliequivalents to

103. Intake was constant at 1,700 ml. per day. In the following three days, in spite of continued administration of beta-hypophamine in increased dosage, the urinary volume rose to 1,720 ml., the daily sodium excretion to 216 and the chloride to 342 milliequivalents. Use of beta-hypophamine was then stopped; the urine volume continued above 2,900 ml. for three days. During the period of beta-hypophamine administration the circulating eosinophil count rose to 428 per cubic millimeter. Four days following cessation of beta-hypophamine administration, the urine volume again dropped to 990 ml. per day and continued below 1,000 ml. On the twenty-fourth hospital day ACTH, 20 mg. every six hours, was again given for a five day period. Sodium and chloride excretion decreased as did the urine volume. The body weight rose 3.5 Kg., and there was evidence of adrenal activation as measured by a drop in the circulating eosinophils. Forty-eight hours after discontinuance of ACTH, the urine volume had risen from 690 ml. per day to 1,460 ml., reaching a peak of 3,290 ml. on the fifth day following cessation of therapy. At this point also the sodium excretion had risen to 256 milliequivalents from 2.1 milliequivalents on the day immediately following cessation. There were concomitant weight loss and disappearance of edema. The eosinophil count following cessation of therapy rose to 355 per cubic millimeter and remained above 100 on subsequent counts. On the fifty-first hospital day, however, the administration of 85 mg. of ACTH produced a drop in eosinophils from 78 to 22 per cubic millimeter.

On the fortieth hospital day he was started on another course of treatment with ACTH, 20 mg. intramuscularly every six hours for fifteen days. During the first eleven days there was an increase in weight of 9.4 Kg. On the eleventh day, however, the urine volume rose to 1,700 ml. from 450 ml. on the initial day of therapy. Thereafter, for five days of continued therapy, the urine volume remained above 2,000 ml., reaching a peak of 3,500 (chart 6). ACTH therapy was discontinued on the fifty-fourth hospital day, and thereafter the urine volume increased even further, reaching a peak of 5,200 on the seventieth hospital day and decreasing to 1,400 on the seventy-third hospital day. With this continued diuresis there was a decided loss of weight and of edema, the patient showing a decrease in weight of 16 Kg. from the time of onset of diuresis on the sixty-first hospital day. This diuresis, which occurred during therapy, was accompanied with large losses of sodium, potassium and chloride. During ACTH therapy, the carbon dioxide-combining power rose to 34.2 millimoles per liter and the serum chlorides fell to 87 milliequivalents per liter, with a drop in the serum potassium to 2.5 and a maintenance of serum sodium levels of 138 milliequivalents per liter. With the diuresis that followed withdrawal of ACTH, however, there was a spontaneous drop in serum carbon dioxide-combining power to 27.2 millimoles and a rise in serum chlorides to 99 milliequivalents per liter on the third day after cessation of treatment. This change occurred in spite of the excretion of chlorides in amounts greater than in the diuresis during therapy. It is of interest that during this four day rebound period daily total potassium excretion was halved. Four days later serum carbon dioxide-combining power was 20.7 millimoles, serum chlorides 102 milliequivalents and serum potassium 4.5 milliequivalents per liter. During the period of therapy and rebound diuresis there was little significant change in the proteinuria. There was, however, a remarkable decrease in the number of casts excreted per twenty-four hours during the period following cessation of therapy, although the latter fact in part may be accounted for by the extremely dilute urine. The serum total protein, however, on the day of discharge had risen to 5.8 Gm., with a serum albumin of 3.8 Gm. in contrast

to a serum total protein level of 4.3 Gm., with 1.3 Gm. of albumin, during the midperiod of therapy. During the peak of the rebound diuretic phase there was tachycardia of 120.

Comment.—This patient illustrates graphically the great loss of edema fluid as urinary water and electrolyte which may occur during adequate prolonged ACTH therapy, and which may further increase following cessation of ACTH therapy if further edema fluid remains to be mobilized. The tachycardia, the drop in serum potassium and chlorides and the elevation of carbon dioxide-combining

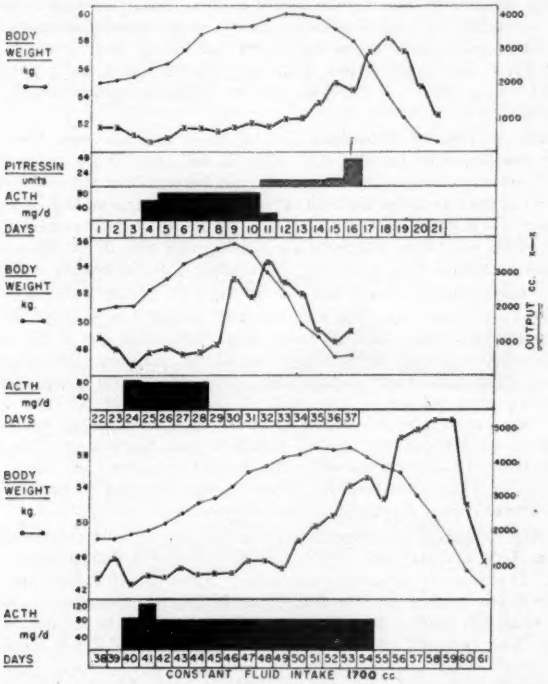

Chart 6 (patient R. G.).—Results of treatment of nephrosis with ACTH.

power are concomitants of this heavy fluid and electrolyte loss. The reversal of the hypochloremic alkalosis during a four day period in which total daily chloride excretion was greater and total daily potassium excretion less than during the treatment period is of interest in view of the speculation concerning the causation of this phenomenon. The drop in eosinophil count during ACTH therapy and the prompt rebound to high levels following cessation of therapy indicate the functional state of the adrenal cortex during these periods.

CASE 6.—L. T., a 17 year old school boy, was treated with 80 to 160 mg. doses of ACTH per day for three weeks.

Six weeks before his admission to this hospital he noted a mild head cold with some dryness of the throat which improved in two days. Five and a half weeks before admission he noted afternoon edema of the ankles, as well as some tightness of his throat. He was admitted to an outside hospital, where he was observed to have a temperature of 102 F., generalized edema, slight ascites and a small right pleural effusion. The white blood cell count was normal, but the serum protein value was low with reversed albumin to globulin ratio. Cholesterol was found to be 440 mg. per hundred milliliters. Urine showed protein (4 +) and normal sediment. Beta hemolytic streptococci were cultured from his throat. He was given penicillin medication, with return of temperature to normal in five days. He was then treated with salt-free human albumin, which caused a moderate diuresis. After that he was transferred to this hospital for further study.

Past history was of significance in that at birth the patient was a "blue baby." This cyanosis gradually disappeared, and no further cardiac abnormality was ever noted.

Results of Physical Examination.—The blood pressure was 124 mm. of mercury systolic and 80 diastolic, respirations 22, pulse rate 70 and the temperature 98 F. There was edema of the face, eyelids and lower part of the back and of the lower part of the legs to the midthigh region. Slight bilateral axillary and inguinal adenopathy was present. Examination of the chest showed a slight amount of fluid at the base of the right lung, and there was demonstrable fluid in the abdomen. The heart was of normal size, and there was a grade I aortic systolic murmur.

Laboratory Data.—Urinary p_H was 6.0, specific gravity 1.030 and protein excretion 6.0 Gm. per day. The spun sediment showed 2 to 4 white blood cells and 1 to 2 granular casts per high power field. Hematocrit was 46 per cent; the corrected erythrocyte sedimentation rate was 30 mm. per hour. White blood cells numbered 7,800, with a normal differential count. Blood urea nitrogen measured 10 mg. and serum protein 3.7 Gm., with 1.5 Gm. of albumin per hundred milliliters. The carbon dioxide-combining power was 25.8 millimoles per liter. Cholesterol was 660 mg. per hundred milliliters, and chlorides were 104, sodium 140, potassium 4.8 and calcium 4.7 milliequivalents per liter; phosphate was 1.6 millimoles per liter. Phenolsulfonphthalein excretion equaled 50 per cent in two hours. Throat culture revealed hemolytic streptococci.

Hospital Course.—The patient was placed on constant diet and constant fluid intake at 1,200 ml. per day. After a suitable control period, administration of ACTH, 20 mg. every six hours, was begun. However, after four days of this schedule it was evident that the dosage was inadequate, since the eosinophil fall was of small magnitude. Therefore, the dosage was raised to 160 mg. of ACTH per day. The eosinophil response was satisfactory the second day of this increased dosage.

The urine output leveled off at about 1,000 ml. for the first five days of therapy, while his weight first dropped and then rose to the initial value. By the sixth day of therapy and the second day of increased dosage the urine volume increased and was maintained at this level or over for the next thirteen days, when it attained the maximum output. His weight during this time had shown a steady decline (chart 7).

The urinary sodium excretion initially declined but then gradually rose until the thirteenth day of treatment. On the fourteenth day 40 units of beta-hypophamine was given with a resultant decrease in urine volume but with a threefold increase in sodium excretion despite the reduced volume. On the fifteenth day he was given 30 mg. of desoxycorticosterone acetate intramuscularly, and with this the urine volume sharply decreased as did the sodium output, though by the seventeenth day

potassium excretion had increased to 81 milliequivalents per day. On the eighteenth day administration of potassium chloride was begun in the amount of 50 milliequivalents per day. The total urinary protein output began to decrease on the ninth day of treatment and had fallen from an initial level of 9.3 Gm. to 1.2 Gm. per day by the eighteenth day of therapy. There was a definite decrease in the twenty-four hour excretion of casts during and following the period of therapy.

At the end of twenty-one days the ACTH treatment was discontinued. The sodium excretion, which had fallen to 20 milliequivelents per day, rose immediately to 146 milliequivalents per day, while the urine volume increased slightly. Potassium excretion, on the other hand, had dropped with cessation of ACTH therapy as did

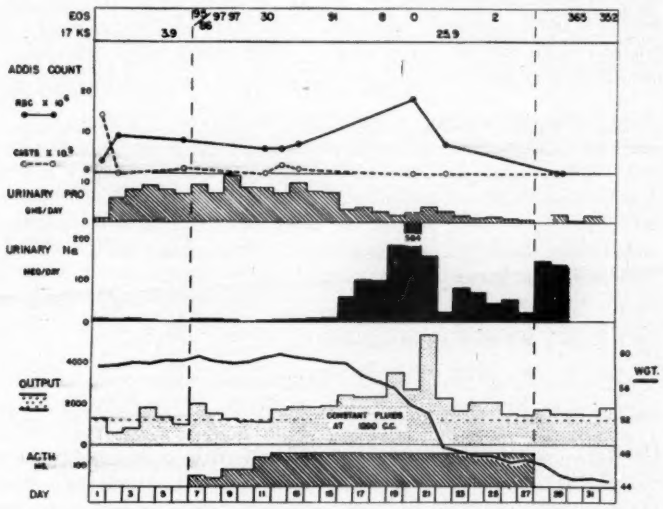

Chart 7 (patient L. T.).—Results of treatment of nephrotic syndrome with ACTH.

the chloride excretion. Proteinuria remained at lower levels of the latter part of the treatment period, i. e., between 0.5 to 1.0 Gm. per day.

The rise in urine volume following cessation of therapy was not as pronounced as had been seen in the edematous nephrotic patients. This may in part be attributable to the fact that the patient had completely lost all signs of edema both by roentgenologic and physical examination.

Comment.—This patient showed a notable electrolyte and water diuresis beginning about the seventh day of ACTH therapy. Administration of beta-hypophamine during this time apparently decreased the urine volume and increased the sodium and chloride excretion, while desoxycorticosterone acetate also given during administration of ACTH decreased the sodium output and increased the potassium excretion. The decreases in proteinuria and cylindruria were definite.

It is of interest to note that in this patient with loss of all evidence of edema on ACTH therapy discontinuance of therapy was not followed by the usual large diuresis of sodium and water typical of the response of the grossly edematous patient.

Studies of the Effect of ACTH and Cortisone on Thyroid Function and Lipid Metabolism in Nephrosis.—The cause of the hypometabolism exhibited by patients with nephrosis is unknown. While the basal metabolic rate is characteristically low in nephrotic patients, other measurements of thyroid activity, such as the I^{131} accumulation gradient and serum protein–bound iodine, do not invariably reveal the presence of hypothyroidism to explain the reduced metabolic state. In 4 patients with low basal metabolic rates Hill [30] reported the I^{131} accumulation gradient to be normal. The serum protein–bound iodine was below normal in 2 of these patients, normal in 1 and increased in the other

TABLE 5.—*Effect of ACTH and Cortisone on Thyroid Function in Nephrosis*

Patient	Age, Yr.	Sex	Treatment		I^{131} Gradient	Serum Protein-Bound Iodine, Micrograms/100 Cc.	Basal Metabolic Rate, %
G. D.	18	M	ACTH, 100 mg./day/7 days....	Before	2.5	0.9	—35
				During	2.0	6.2	—24
R. G.	15	M	ACTH, 80 mg./day/7 days.....	Before	3.1	20.0	—25
				During	7.6	7.2	—36
H. D.	26	M	Cortisone, 100 mg./day/10 days	Before	0.9	1.5	....
				During	0.7	2.5	....
J. P.	15	M	ACTH, 80 mg./day/7 days.....	Before	1.0	5.8	—15
				During	4.4	3.6	—11
				Normal	1.0 to 10	3.5 to 8.0	

(table 5). The administration of ACTH or cortisone to these patients altered these indexes of thyroid activity but not the basal metabolic rate. For example, 2 patients (J.P. and R.G.) showed an elevation of the I^{131} accumulation gradient with ACTH treatment. During the same period, however, one of these patients, R.G., with initial serum protein–bound iodine of 20.0 micrograms per hundred milliliters had a fall to a normal level of 7.2 micrograms per hundred milliliters. Another patient, G.D., had an elevation of the serum protein–bound iodine from 0.9 to 6.2 micrograms and no decrease in urinary protein–bound iodine. Therefore, in this patient the rise cannot be attributed to a decreased excretion of protein–bound iodine. Since the excretion of thyroid-stimulating hormone in the urine was not followed, no statement regard-

30. Hill, S. R., Jr.; Forsham, P. H.; Roche, M., and Thorn, G. W.: The Response of the Adrenal Cortex and Thyroid Gland to ACTH and Cortisone in Patients with Hypothyroidism and the Nephrotic Syndrome, abstracted, J. Clin. Endocrinol., to be published.

ing the effect of ACTH treatment on excretion of this hormone can be made. In normal subjects given ACTH or cortisone there is a fall in the I^{131} accumulation gradient and the serum protein-bound iodine, in contrast to nephrotic patients in whom there tends to be an increase in the I^{131} gradient and an elevation of the serum protein-bound iodine when the latter value is initially very low. These observations suggest that the existing state of the secretion of adrenal steroids by nephrotic patients may influence the state of thyroid activity

Studies of the respiratory quotient in 3 nephrotic patients (R.G., G.D. and J.P.) showed a transient fall in nonprotein respiratory quotient, followed by a rise to very high levels, often reaching a value of 1.00, in contrast to patients with Addison's disease and normal subjects, who show a more sustained fall in respiratory quotient when given cortisone (Addison's disease) [31] or ACTH (normal).[32]

The existence of elevated serum lipids in patients with nephrosis is well known. Changes in the serum lipids of 3 of these nephrotic patients treated with ACTH were studied by Kahn and his associates.[33] There was initially a rise in serum phospholipids and free cholesterol with a later fall, although administration of ACTH was continued. The cholesterol esters also showed an initial rise in 2 of these patients, but in the third patient there was a continuous fall during ACTH administration. These investigators have not observed an immediate fall in cholesterol esters in all subjects, nephrotic or nonnephrotic, treated with ACTH.

Summary of the Nephrotic Cases.—In 2 patients in whom cortisone was used, little effect was observed on the course of the disease or edema. In striking contrast was the response of 4 patients to the administration of ACTH. In each case cessation of therapy after periods of as little as two days resulted in a dramatic increase in the excretion of sodium, chloride and water, with concomitant loss of edema and body weight. This effect was also observed during continued treatment with ACTH, in which case sodium and water diuresis began on the seventh to tenth day of therapy and continued for four to five days. Discontinuance of administration of ACTH at this point resulted in further diuresis of varying degree, possibly depending on the amount of edema fluid remaining.

31. Forsham, P. H.; Bennett, L. L.; Roche, M.; Reiss, R. S.; Slessor, A.; Flink, E. B., and Somerville, W.: Clinical and Metabolic Changes in Addison's Disease Following the Administration of Compound E Acetate, Tr. A. Am. Physicians **62**:233, 1949.

32. Roche, M. R., and Frawley, T.: Unpublished data.

33. Kahn, S.; Roche, M. R.; Emerson, K. E., Jr., and Thorn, G. W.: The Effect of ACTH and Cortisone on Blood Lipid Levels and Respiratory Quotient in Man with Particular Reference to the Nephrotic Syndrome, to be published.

In 3 instances the administration of ACTH was accompanied with a definite decrease in proteinuria and a decrease in the number of casts excreted in the urine during a twenty-four hour period.

The administration of beta-hypophamine and of desoxycorticosterone acetate during the diuretic phase appeared each to exert its characteristic effect on electrolyte and water excretion, although this varied with the degree of the diuresis. A decrease in the serum chloride and an increase in the serum carbon dioxide–combining power was observed in 2 of the patients during ACTH therapy.

Studies have been made on serum protein–bound iodine content and accumulation gradient of I^{131}. The accumulation gradient was normal in all patients, and an elevation occurred in 2 with ACTH and cortisone. ACTH and cortisone administration caused a rise in low levels of protein-bound iodine and a decrease in normal levels. Studies of the nonprotein respiratory quotient in 3 nephrotic patients on ACTH therapy showed an initial fall with reduced oxygen consumption, followed by a reversal of these effects about the sixth day of therapy. Similarly, 2 patients showed an initial rise in serum phospholipid and free cholesterol, which later fell on continued ACTH administration.

There is no evidence to date to indicate that the cause of the nephrotic syndrome has been permanently affected by cortisone or ACTH. It is true that the degree of proteinuria has been decidedly reduced in certain instances following diuresis associated with ACTH therapy.

IV. LUPUS ERYTHEMATOSUS DISSEMINATUS AND DERMATOMYOSITIS

Six patients with lupus erythematosus disseminatus had evidence of renal disease manifested by albuminuria and hematuria. They were treated with ACTH in doses of not less than 100 mg. daily, the total dose ranging from 900 to 7,500 mg. From one to four courses of treatment were given, a single course usually lasting for a two week period. In 2 of the patients the disease was of the acute type, and all but one were female. With the exception of a slight reduction in the gross hematuria which was present in one patient, ACTH failed to alter appreciably the renal changes. Proteinuria persisted, although all other evidences of activity of the disease showed a favorable response.

Three patients with dermatomyositis have been treated with ACTH and cortisone. Proteinuria was present in all patients. In spite of an otherwise satisfactory response to ACTH, there was no reduction in the albuminuria.

COMMENT

Available evidence in animals indicates that adrenal steroids may inhibit the development of lesions which are secondary to a hyperimmune

reaction.[34] In some instances, however, anaphylaxis is not prevented by ACTH,[35] nor is the Arthus reaction prevented in rabbits given injections of normal horse serum.[36] Nephritis, which has long been linked in man with a hyperimmune reaction to the beta hemolytic streptococcus, can be produced in the rat by the injection of anti-rat-kidney rabbit serum. This nephritis, however, cannot be prevented by the administration of cortisone to either the intact or the adrenalectomized rat.[37] Further, it has been shown that both spontaneous and induced proteinuria in the rat may be greatly decreased by adrenalectomy and reestablished by administration of desoxycorticosterone acetate and cortisone.[38] This occurs even though renal blood flow and glomerular filtration in the rat are not affected by adrenalectomy, according to some workers.[39] Our findings in patients with acute and subacute glomerulonephritis are not surprising in the light of these observations. It is of interest, however, that Farnsworth[40] demonstrated in 2 patients with subacute nephritis a decrease in hematuria, as well as a decrease in both blood pressure and blood urea nitrogen, on ACTH therapy. A third patient with acute glomerulonephritis showed disappearance of hematuria on the fifth day following ACTH therapy. Since the course of acute nephritis, particularly in children, tends to be toward complete healing, it is difficult to evaluate this last case and those presented in our protocol. Our observations in cases of subacute nephritis, however, are at variance, and further study must be done to clarify the situation. In 2 of our patients (R.K and T.O'T.) there was an increase in nitrogen retention, and in R.K. a decided elevation of blood pressure occurred in spite of

34. Berthrong, M.; Rich, A. F., and Griffith, P. C.: Study of Effect of Adrenocorticotropic Hormone (ACTH) upon Experimental Cardiovascular Lesions Produced by Anaphylactic Hypersensitivity, Bull. Johns Hopkins Hosp. **86**:131, 1950. Clampit, J.: Chemotherapy of Allergic Arteritis in Rabbit, Federation Proc. **9**:263, 1950.

35. Leger, J.; Leith, W., and Rose, B.: Effect of Adrenocorticotrophic Hormone on Anaphylaxis in Guinea Pig, Proc. Soc. Exper. Biol. & Med. **69**:465, 1948.

36. Harris, S., and Harris, T. N.: Effect of Cortisone on Some Reactions of Hypersensitivity in Laboratory Animals, Proc. Soc. Exper. Biol. & Med. **74**:186, 1950.

37. Knowlton, A. I.; Loeb, E. N.; Stoerk, H. C., and Seegal, B. C.: Development of Hypertension and Nephritis in Normal and Adrenalectomized Rats Treated with Cortisone, Proc. Soc. Exper. Biol. & Med. **72**:722, 1949.

38. Addis, T.; Marmorston, J.; Goodman, H. C.; Sellers, A. L., and Smith, M.: Effect of Adrenalectomy on Spontaneous and Induced Proteinuria in the Rat, Proc. Soc. Exper. Biol. & Med. **74**:43, 1950.

39. Lotspeich, W. D.: The Effect of Adrenalectomy on the Renal Tubular Reabsorption of Water in the Rat, Endocrinology **44**:314, 1949. Friedman, S. M.; MacKenzie, K. R., and Friedman, C. L.: Renal Function in the Adrenalectomized Rat, ibid. **43**:123, 1948.

40. Farnsworth, E. B.: Acute and Subacute Glomerulonephritis Modified by Adrenocorticotropin, Proc. Soc. Exper. Biol. & Med. **74**:57, 1950.

remarkable clearing of the concomitant skin lesions. In one patient with subacute nephritis the appearance of hematuria during ACTH therapy was disappointing, while in 4 others an increase in hematuria following omission of the drug may have attested to some beneficial effect. In 2 patients (P.O'B and T.O'T.) definite diminution in the skin reaction to the hemolytic streptococcus occurred, in spite of indefinite effect on the renal disease. These observations stimulate speculation concerning the possible difference in the role of hyperimmune reaction and inflammatory response in nephritis and other "collagen diseases." Of interest in this regard is the recent publication by Weinstein,[41] who observed clinical manifestations of glomerulonephritis following streptococcic pharyngitis in patients in whom infection had been so rapidly eliminated by penicillin that no antibacterial or antitoxic immunity could be demonstrated.

The role of ACTH and cortisone in decreasing this inflammatory response and the fibroblastic reaction [42] has been pointed out. It is possible that this may be of benefit in the early stages of acute nephritis, although its only clinical manifestation is a disappearance of grossly bloody urine without affecting microscopic hematuria. That such an effect may possibly be of benefit in the anuria of acute nephritis or in the prevention of subsequent fibrosis and destruction of glomeruli with functional impairment must await careful study of a far greater series of cases.

The mechanism by which edema fluid accumulates in patients with nephrotic syndrome is poorly understood. Although proteinuria and hypoproteinemia are contributory factors, they are by no means the whole story. It is well known that a spontaneous diuresis may occur without demonstrable change in serum protein level or in the degree of proteinuria. It has also been shown that certain procedures may initiate a diuresis, for example, the induction of measles [43] or the administration of nitrogen mustards.[44] It is an attractive hypothesis to consider that many of the nonspecific mechanisms concerned with the initiation of

41. Weinstein, L.; Bachrach, L., and Boyer, N. H.: Observations on the Development of Rheumatic Fever and Glomerulonephritis in Cases of Scarlet Fever Treated with Penicillin, New England J. Med. **242**:1002, 1950.

42. Creditor, M. C.; Bevans, M.; Mundy, W. L., and Ragan, C.: Effect of ACTH on Wound Healing in Humans, Proc. Soc. Exper. Biol. & Med. **74**:245, 1950. Ragan, C.; Howes, E. L.; Plotz, C. M.; Meyer, K., and Blunt, J. W.: Effect of Cortisone on Production of Granulation Tissue in Rabbit, ibid. **72**:718, 1949.

43. Janeway, C. A.; Moll, G. H.; Hallman, M.; Barnett, L. A., and Metcoff, J.: Management of the Nephrotic Syndrome in Children, Bull. New England M. Center **11**:5, 1949.

44. Chasis, H.; Goldring, W., and Baldwin, D.: Effect of Febrile Plasma, Typhoid Vaccine, and Nitrogen Mustard on Renal Manifestations of Human Glomerular Nephritis, Proc. Soc. Exper. Biol. & Med. **71**:565, 1949.

diuresis in patients with the nephrotic syndrome may in part, at least, involve the pituitary-adrenal system and may in fact be simulated by the administration of ACTH.

The mechanism by which the administration of ACTH and the increased release of adrenal steroids initiates a diuresis is also not yet understood. The simplest case is that in which ACTH is given for five to seven days with some sodium and water retention, followed by a prompt diuresis twenty-four to forty-eight hours after ACTH is withdrawn. At first thought this might be considered to be due to a temporary state of adrenocortical inactivity (insufficiency) following excessive stimulation of the cortex with relatively large doses of ACTH. This hypothesis is supported by the fact that no appreciable increase in potassium excretion is observed despite the magnitude of the diuresis and by the fact that the eosinophil content returns rapidly to normal or supranormal level. Changes in 17-ketosteroid excretion are difficult to interpret because of the increased urine volume which so characteristically accompanies a diuresis

That this mechanism is not the whole story is suggested by the fact that cortisone treatment in a dosage which has been shown to be a potent inhibitor of endogenous adrenal secretion is not followed by as significant a diuresis as occurs following the administration of large doses of ACTH. Furthermore, during the sodium diuresis which follows ACTH withdrawal, a reduced sensitivity to desoxycorticosterone administration occurs, in contrast to the greatly increased sensitivity observed in patients with Addison's disease. Thus, very large doses of desoxycorticosterone acetate (20 to 40 mg.) do not elicit the extremely low urinary sodium values observed in patients with uncomplicated adrenocortical insufficiency similarly treated. This reduced effectiveness is also true of posterior pituitary hormone administered every two to three hours round the clock. These facts and the observation of Conn [45] on the reduced glucose threshold of normal subjects treated with large doses of ACTH suggest tubular "fatigue" or decreased responsiveness to hormone action as an important adjunct in explaining the diuresis which follows withdrawal of ACTH.

The theory of "renal tubular fatigue" or altered responsiveness to adrenal steroids, posterior pituitary hormone and, possibly, parathormone in the presence of continued administration of ACTH or cortisone gains further support from studies carried out by Wilson [46] in our laboratory. He demonstrated increased capacity of patients with Cushing's syndrome

45. Conn, J. W.; Louis, L. M., and Johnston, M. W.: The Effects of Intravenous Reduced Glutathione (GSH) upon Glycosuria and Hyperglycemia Induced in Man by Adrenocorticotropic Hormone (ACTH), J. Clin. Investigation **28**:775, 1949.

46. Wilson, D. L.: Personal communications to the authors.

to eliminate a test sodium load following administration of desoxycorticosterone acetate. We have also observed a diabetes insipidus–like syndrome with reduced response to pituitary extract in a patient with Cushing's syndrome in the absence of pituitary tumor or enlargement of the sella turcica.

The delay in the onset of diuresis (twenty-four hours) after ACTH is withdrawn supports the importance of relative adrenal insufficiency in contrast to "tubular" fatigue or refractiveness since a rapid regression in adrenocortical steroid elaboration follows the withdrawal of ACTH. The combination of tubular "fatigue" and relative adrenal insufficiency would, of course, lead to tremendous salt and water excretion in patients with increased plasma volume and large quantities of extracellular fluid available for excretion. In patients, such as L.T., in whom evidence of excess extracellular fluid had disappeared, such a diuresis did not occur, possibly because of the inavailability of excess extracellular fluid and electrolyte. A similar failure of response to the blocking of tubular mechanisms for resorption of salt and water in the absence of abundantly available electrolyte and water has been observed by Pitts.[47]

Certainly the more complex situation, namely, the sodium and water diuresis which occurs while patients are continuing to receive ACTH in large doses with all indications of excellent adrenocortical activation, cannot be attributed to adrenocortical insufficiency. Here one must postulate renal tubular "fatigue" or the competitive effect of cortisone-like steroids on the action of desoxycorticosterone-like steroids, as well as the possible effect of cortisone-like steroids on posterior pituitary secretion and hormonal action. It is also possible that the increased glomerular filtration function which has been demonstrated in patients treated with ACTH [48] may be an important factor in conjunction with the aforementioned mechanisms. It is obvious, however, that adrenocortical insufficiency cannot be evoked as a possible explanation of the sodium diuresis in the presence of greatly increased adrenal steroid secretion during ACTH therapy, unless quantitative changes in the type of steroid elaborated (i. e., 11-desoxycorticosterone, 11-17-oxysteroid) are postulated.

At this point in our studies we are inclined to believe that the diuresis of sodium and water which occurs in patients with nephrotic syndrome during ACTH treatment is accounted for by (1) renal "tubular fatigue" with reduced sensitivity to adrenal sodium-retaining hormone as a con-

47. Duggan, J. J.; Pitts, R. F.; Miner, P., and Barrett, M.: Studies on Diuretics: I. The Site of Action of Mercurial Diuretics, J. Clin. Investigation **26**:365, 1950.

48. Ingbar, S. H.; Ralman, A. S.; Burrows, B. A.; Kass, E. H.; Sisson, J. H., and Burnett, C. H.: Changes in Normal Renal Function Resulting from ACTH and Cortisone, J. Clin. Investigation, to be published.

sequence of prolonged high level of 11-17-oxysteroid secretion and/or competitive action of 17-oxysteroids on 11-desoxy-like steroids as a result of a qualitative change in the ratio of steroids secreted by the adrenal cortex under ACTH administration, the (2) increased glomerular filtration fraction during ACTH therapy aided by the tremendous excess of extracellular fluid and electrolyte available for excretion and (3) the enhancement of these effects by temporary adrenocortical insufficiency following the withdrawal of ACTH or cortisone therapy.

Finally, the persistence of diuresis and the disappearance of protein in the urine, when it occurs following ACTH administration, involve mechanisms of repair at present poorly understood but aided by the reduction in over-all tissue edema.

CONCLUSIONS

There is no conclusive evidence in the small series of patients comprising this study that ACTH and cortisone exert any beneficial effect on the over-all course of acute, subacute and chronic nephritis.

ACTH therapy appears to be an effective method of inducing a diuresis in patients with the nephrotic syndrome. Often a diuresis may be induced by a relatively short period of treatment. The differences in mechanism involved in the diuresis occurring twenty-four to forty-eight hours after cessation of a short period of therapy with ACTH as contrasted with the diuresis occurring during a more prolonged ACTH administration are described and discussed.

Metabolic studies carried out in patients with nephrosis treated with ACTH and cortisone revealed differences in the response of respiratory quotient, thyroid function, cholesterol and phospholipid levels from the response under similar conditions in normal persons and in patients with Addison's disease.

ADDENDUM

Since submission of this manuscript, 4 additional patients with renal disease have been treated with ACTH. All were studied while receiving a constant diet and fluid intake, and all showed adequate evidence of adrenocortical stimulation, as evidenced by a drop in circulating eosinophils and increased excretion of urinary 17-ketosteroids.

CASE 1.—A 42 year old man with acute glomerular nephritis and complete anuria was treated with ACTH, 100 mg. daily, for five days during the second week of his anuria. There was no change in his clinical course, nor was there resumption of urine flow. Autopsy observations at the end of five weeks of anuria confirmed the diagnosis of acute glomerular nephritis.

CASE 2.—A 43 year old woman with seven weeks of gross hematuria following the onset of acute glomerular nephritis was treated with ACTH, 100 mg. daily, for nine days. On the fifth day of therapy gross hematuria disappeared, but microscopic hematuria (Addis count) persisted unchanged during the remainder of the treatment period. Two days following cessation of treatment, gross hematuria again reappeared but decreased spontaneously to microscopic levels during the next ten days. Tonsillectomy two weeks later caused recurrence of gross hematuria, in spite of ACTH administration before, during and after the procedure. There was no change in erythrocyte sedimentation rate, the slight elevation of temperature or blood urea nitrogen during the original nine day treatment period. The phenol-

sulfonphthalein excretion and glomerular filtration rate (as measured by the clearance of sodium thiosulfate) were decreased initially and were unaffected by therapy.

CASE 3.—A 46 year old man with chronic glomerular nephritis and nephrotic syndrome was treated with ACTH, 100 mg. daily for eleven days, then 160 mg. daily for four days, for a total treatment period of fifteen successive days. No diuresis occurred during the treatment period, but an effective diuresis with loss of edema took place following cessation of therapy. The initial blood urea nitrogen of 43 mg. per hundred milliliters rose to 92 mg. on the sixth day of treatment but fell to control levels during the latter part of the treatment period, and to 19 mg. three days after cessation of ACTH administration. The initial blood pressure of 160 systolic and 110 diastolic fell to 135 systolic and 70 diastolic on rest in bed only and remained at the latter level during ACTH treatment.

CASE 4.—A 43 year old man with chronic glomerular nephritis and nephrotic syndrome with massive edema was treated with ACTH, 100 mg. daily for twelve days, then 160 mg. daily for three days, for a total period of fifteen successive days. No diuresis occurred during administration of the hormone, and a clinically insignificant rise in urine volume was noted for two days after cessation of treatment. During the treatment period blood urea nitrogen rose from 11 mg. per hundred milliliters to 67 mg. and returned to 30 mg. two weeks after treatment was stopped. A decreased glomerular filtration rate (sodium thiosulfate clearance) and subnormal phenolsulfonphthalein excretion were unchanged by treatment. During the fifteen day treatment period the serum sodium level fell from 140 milliequivalents per liter to 126 and the serum chloride concentration from 103 milliequivalents to 86. This change could largely be accounted for by the external balance of sodium chloride and water, however. Two weeks later, a second course of treatment with ACTH, 100 mg. daily for six days, during which serum sodium and chloride values were maintained at normal levels, resulted in no significant change in urine output.

NITROGEN SHIFT IN CANCER

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TISSUE wasting in the presence of progressive tumor growth is a common observation. Weight loss, however, does not always appear early in cancer. Other signs of deranged nitrogen metabolism, such as hypoproteinemia, may persist for some time while synthesis of tissue proteins is taking place.[1] The study here reported was undertaken in an attempt to explore further the shifts in nitrogen utilization occurring in patients with neoplastic disease, especially when protein hyperalimentation was employed.

EXPERIMENTAL STUDIES

Material.—Two patients from the Third Medical Division at Bellevue Hospital, New York, were studied, the first for one period, the second for four periods. H. W. was a 51 year old Chinese man with bronchogenic carcinoma which had been diagnosed by biopsy of a supraclavicular node. There were widespread metastases to ribs, vertebrae, pelvic bones and lymph nodes. The course was rapidly downhill and the twenty-one day study period was terminated by death.

The second patient, a 70 year old white man, O. P., had a space-occupying retro-orbital lesion and a progressively enlarging liver which finally occupied two thirds of the abdomen. Repeated punch biopsy specimens of the liver were reported as malignant tumor, type undetermined. The patient periodically signed out of the hospital only to return when he felt worse. His study was, therefore, divided into four periods, the last of which was terminated by death.

During these periods nitrogen balance records were kept on both patients. Routine blood counts, plasma protein determinations and blood volume studies were done at regular intervals. An attempt was made to maintain the protein intake at as high a level as possible. This could not be accomplished with H. W. O. P., however, was kept on a high protein diet, at times supplemented by administration of protein hydrolysates, until the last period, when serious anorexia developed.

Methods.—Several methods for handling the diet were tried. Because of the extremely erratic appetites which these patients exhibited, it was impossible to plan a fixed diet and expect complete consumption. The most satisfactory method was to weigh each plate of food before and after the meal. Separate plates were used for each article of food. Diet composition was calculated from the tables of McCance and Widdowson,[2] as well as other standard tables. When figures were unavailable

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1. Homburger, F., and Young, N. F.: Studies on Hypoproteinemia: I. Hypoproteinemia in Patients with Gastric Cancer; Its Persistence After Operation in the Presence of Body Tissue Repletion, Blood **3**:1460, 1948.

2. McCance, R. A., and Widdowson, E. M.: The Chemical Composition of Foods, ed. 2, New York, The Chemical Publishing Company, Inc., 1947.

for a specific food, the nitrogen content was chemically determined by a modified micro-Kjeldahl nesslerization method.

Urine was collected in twenty-four hour lots and preserved by refrigeration and addition of toluene. Fecal nitrogen was calculated as 15 per cent of total nitrogen intake.

Blood counts were done in the routine manner (always by the same technician). Hemoglobin determinations were made on a Klett-Summerson photoelectric colorimeter. Hematocrit (packed red cell volume) was estimated by the Wintrobe method.[3] Plasma protein determinations were made by the same modified micro-Kjeldahl nesslerization method employed for food and urine. Plasma volume was measured by the Evans blue (T-1824) dye method, using a single blood sample as recommended by Gregersen.[4] Figures for total circulating hemoglobin and plasma protein were derived from the aforementioned data.

TABLE 1.—*Results of Blood Counts and Protein Determinations Made at Beginning and End of Each Study Period on Patients H. W. and O. P.*

Patient and Period		Date	Hb., Gm./ 100 Cc.	R.B.C., Millions	Hematocrit	M.C.V., Cu. μ	M.C.Hb., Gm.	M.C.Hb.C., %	Total Protein, Gm./ 100 Cc.	Plasma Albumin, Gm./ 100 Cc.	Plasma Globulin, Gm./ 100 Cc.
H. W.	1	3/19/48	9.63	3.61	32	88	27	30	6.20	3.79	2.41
		4/ 8/48	10.10	3.23	29	89	31	34	6.96	3.64	3.32
O. P.	1	11/ 3/47	11.06*	3.34	39	116	32	28	6.79	4.24	2.55
		11/24/47	11.86	3.32	40	120	35	29	6.40	4.42	1.98
	2	1/13/48	4.85	1.80	17	94	27	28	5.29	3.33	1.96
		2/ 4/48	6.61	2.25	23	102	29	28	5.98	3.69	2.29
	3	3/16/48	5.60	2.36	24	101	23	23	7.58	3.73	3.85
		4/ 8/48	7.29	3.09	24	78	23	30	7.46	3.75	3.71
	4	5/ 7/48	5.63	2.33	22	94	24	25	6.50	3.16	3.34
		6/ 8/48	3.80	1.38	12	87	27	31	5.26	2.36	2.90

* Sharp fall in hemoglobin concentration between periods 1 and 2 can be explained by development of melena during a month's absence from the hospital.

RESULTS

In table 1 are listed the blood counts and results of plasma protein determinations done at the beginning and end, only, of each study period. H. W. had a normocytic, normochromic type of anemia which did not change appreciably throughout the single period during which he was studied. The total plasma protein concentration increased, because of an increase in globulin, but the plasma albumin fraction actually declined.

During his first study period O. P. had a macrocytic, normochromic blood picture strongly resembling that seen in cirrhosis.[5] The reaction to the cephalin flocculation test fluctuated among weakly positive, negative and positive. The patient went home after the first period and returned to the hospital because of weakness and dizziness. He described one

3. Wintrobe, M. M.: Clinical Hematology, Philadelphia, Lea & Febiger, 1942.

4. Gregersen, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824: Survey of Present Basis of Dye-Method and Its Clinical Applications, J. Lab. & Clin. Med. **29**:1266, 1944.

5. Bateman, J. C.; Shorr, H. M., and Elgvin, T.: Hypervolemic Anemia in Cirrhosis, J. Clin. Investigation **28**:539, 1949.

tarry stool. The reactions to repeated guaiac tests on stool specimens were strongly positive at this time. Edema of the lower extremities extended to the sacral region and was progressive during the second study period. Although plasma protein concentration increased somewhat, there appeared to be lag in edema formation and subsequent resorption. As pointed out by Burch,[6] such lag could be explained by lowered tissue pressure resulting from stretching of the fibrous network. Increased protein left by receding edema fluid could also presumably increase the osmotic pressure of extracellular fluid to the point of slowing edema resorption, especially in the presence of a borderline plasma protein level. A sharp reduction in hemoglobin concentration indicated that bleeding was more massive than suggested by the clinical history. There was reduction, too, in the degree of macrocytosis, which again is comparable to similar events (i. e., bleeding) in cirrhotic patients.

During the third study period improvement in hemoglobin concentration and red blood cell count was partially attributable to a transfusion of 500 cc. of whole blood. The improvement in plasma protein was largely due to increase in the globulin fraction. (The mechanism of a decrease in plasma albumin accompanied with an increase in plasma globulin, not uncommonly seen in patients with cancer, is hard to explain.) Malnutrition was probably not operating in this case, since O. P. was on a high protein diet and in positive nitrogen balance at this time. The extensive involvement of the liver was undoubtedly a factor, perhaps acting to prevent proper utilization of nutrients. The fourth period was characterized by rapid decline. Anemia increased and plasma albumin fell.

Table 2 shows the average daily caloric and protein intake. The total grams of nitrogen retained or lost per period is given in column 9. Blood volume determinations were made at the beginning of each period and on two occasions at the end of the period. Total circulating hemoglobin and plasma protein were calculated at the beginning and end of each period. The amount of gain or loss in nitrogen was considered to be 16 per cent of the gain or loss in hemoglobin and plasma protein. The change in weight for each period is listed in column 20. The nitrogen gained or lost due to change in weight was considered to be 3 per cent of the body weight, except in the second and third periods of study on O. P. During these periods roughly half the weight change was adjudged from clinical findings to be due to increase in edema. Nitrogen content of edema fluid was calculated as 0.1 Gm. per hundred cubic centimeters. Changes in body weight were corrected for changes in blood volume.

During the fourth period the rapid wasting appeared to be entirely attributable to tissue loss. It was necessary to use arbitrary figures, since determinations of the volume of extracellular fluid were not made. In the final column are figures for unaccountable nitrogen. Unaccountable

6. Burch, G. E., and Sodeman, W. A.: The Estimation of the Subcutaneous Tissue Pressure by a Direct Method, J. Clin. Investigation **16**:845, 1937.

nitrogen is the nitrogen contributed by intake (less output) and not utilized to form new hemoglobin, plasma protein or body tissue. Loss in hemoglobin, plasma protein and/or body tissue, at times, contributed to this pool of nitrogen.

TABLE 2.—*Pertinent Data Derived from Five*

Patient and Period	Age, Yr.	Sex	Diagnosis	Period of Observation, Days	Average Daily Intake		Transfusion Nitrogen, Gm.	Nitrogen Balance for Period, Gm.	Blood Volume, Cc.	
					Calories	Protein, Gm.			Beginning	End
H. W. 1	51	M	Bronchogenic carcinoma	21	832	31	..	+ 6	4,020	..
O. P. 1	70	M	Malignant tumor, type undetermined	21	2,600	119 ‡	..	+ 168	6,610	..
2	..	..	.....	20	2,532	106	12	+ 111	6,775	7,355
3	..	..	.....	21	2,709	107	..	+ 91	7,502	..
4	..	..	.....	27	1,214	40	..	— 49	6,850	6,765

* Allowance was made for edema and change in blood volume.
† Calculated on basis of first blood volume.
‡ Protein hydrolysate supplement given November 18 to 25.
§ Considered as partially from edema fluid and partially from tissue protein.

Table 3 lists, in the left column, the available nitrogen and its sources for each study period. On the right is the amount of nitrogen utilized in the formation of new hemoglobin, additional plasma protein and increase in body tissue or edema. For each period there was a variable amount of nitrogen retained in the body, the destination of which was unaccountable. Even when the patient was in negative nitrogen balance, as in the fourth period (O. P.), the nitrogen excreted was less than the sum of the nitrogen available from decreases in hemoglobin concentration, plasma protein and weight.

In the figure an attempt has been made to demonstrate graphically the shift of nitrogen for each period. The paired columns represent available nitrogen and disbursed nitrogen for each period. These columns must balance each other.

COMMENT

In these studies it became apparent that, regardless of the state of nitrogen balance of the patient, nitrogen was lost into the body. This loss has been labeled unaccountable nitrogen. A nitrogen-rich tissue must have been expanding at the expense of some nitrogen-poor body compartment. Homburger[7] showed that implantation of sarcoma 180 in mice caused hyperplasia of the lymph nodes, with a significant shunting of nitrogen into lymphoid tissue. Other workers have demonstrated depletion of lymphoid nitrogen in other species. The utilization of exces-

7. Homburger, F.: Studies on Hypoproteinemia: III. Lymphoid Hyperplasia and Redistribution of Nitrogen Caused in Mice by Transplanted Tumors (Sarcoma 180 and Breast Adenocarcinoma E0771), Science **107**:648, 1948.

sive amounts of nitrogen by the lymphatic system in patients with cancer is an attractive theory, particularly in view of the fact that regional hyperplasia, even in the absence of metastases, has long been noticed by some pathologists.[8]

Periods of Study on Patients H. W. and O. P.

Total Gm. Hemoglobin		Nitrogen Used or Lost in Hemoglobin, Gm.*	Total Plasma Protein, Gm.		Nitrogen Used or Lost in Plasma Protein, Gm.*	Weight, Kg.			Nitrogen Used or Lost in Changing Body Weight, Gm.*	Approximate Unaccountable Nitrogen, Gm.
Beginning	End		Beginning	End		Beginning	End	Difference		
387	406 †	+ 3.0	141	158 †	+ 2.7	53.5	52.5	— 1.0	— 20	30.3
731	784 †	+ 8.5	282	266 †	— 2.5	56.7	57.7	+ 1.0	+ 20	122.0
328	486	+ 25.2	297	337	+ 6.4	59.0	61.7	+ 2.7	+ 34 ‖	57.4
420	547 †	+ 20.3	432	425 †	— 1.1	55.9	58.2	+ 2.3	+ 35 ‖	36.8
386	219	— 26.7	352	266	— 13.7	57.5	54.5	— 3.0	— 57	48.4

TABLE 3.—*Summary of Nitrogen Utilization During Five Study Periods in Patients H. W. and O. P.*

Patient	Period	Available Nitrogen, Gm.*		Disbursed Nitrogen, Gm.†	
H. W.	1	Positive nitrogen balance	6.0	Hemoglobin formation	3.0
		Weight loss	30.0	Plasma protein formation	2.7
				Unaccountable nitrogen	30.3
		Total	36.0	Total	36.0
O. P.	1	Positive nitrogen balance	168.0	Hemoglobin formation	8.5
		Plasma protein loss	2.5	Weight gain	30.0
				Unaccountable nitrogen	132.0
		Total	170.5	Total	170.5
	2	Positive nitrogen balance	111.0	Hemoglobin formation	25.2
		Transfusion	12.0	Plasma protein formation	6.4
				Weight gain (½ edema)	34.0
				Unaccountable nitrogen	57.4
		Total	123.0	Total	123.0
	3	Positive nitrogen balance	91.0	Hemoglobin formation	20.3
		Plasma protein loss	1.1	Weight gain (½ edema)	35.0
				Unaccountable nitrogen	36.8
		Total	92.1	Total	92.1
	4	Hemoglobin loss	26.7	Negative nitrogen balance	49.0
		Plasma protein loss	13.7	Unaccountable nitrogen	48.4
		Weight loss	57.0		
		Total	97.4	Total	97.4

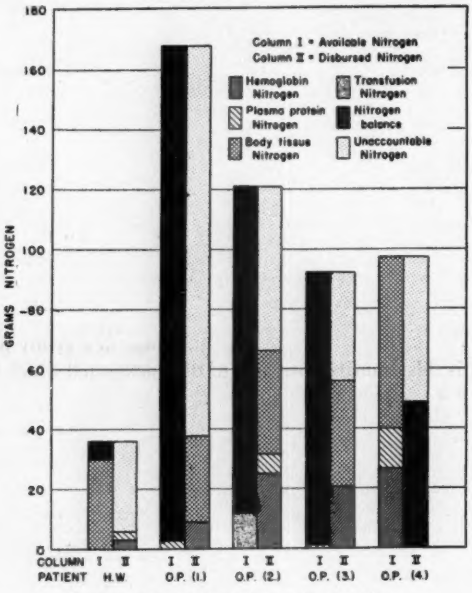
* Sources were diet (excess nitrogen intake over excretion), blood transfusion and loss of hemoglobin, plasma protein and weight.

† Disbursed nitrogen must equal available nitrogen. It is used to form new hemoglobin, new plasma protein and new body tissue or edema fluid.

The total nitrogen content of the body is generally considered to be in the neighborhood of 3 per cent. Analysis by the micro-Kjeldahl nesslerization method of pieces of carefully weighed tumor tissue obtained at surgical intervention and at autopsy gave an average of 2.94 Gm.

8. Terplan, K. L.: Personal communication to the author.

of nitrogen per hundred cubic centimeters, with a range of 2.26 to 4.2 Gm. on nine specimens. Blocks of fatty tissue obtained in the same way contained an average of 0.59 Gm. of nitrogen per hundred cubic centimeters. An increase in tumor tissue, with a simultaneous shrinkage of nitrogen-poor fatty connective tissue, could therefore be contributing to the shift in content of body nitrogen. This process could proceed with relatively little change in total body weight.



Graphic presentation of data from table 3.

SUMMARY AND CONCLUSIONS

Two patients with neoplastic disease were observed for five periods, during which studies were made of nitrogen balance and of changes in total hemoglobin concentration, total plasma proteins and body weight.

In each period a certain portion of nitrogen made available by diet (excess intake over output), by diminution of hemoglobin and plasma protein, by blood transfusion or by loss of weight, could not be accounted for by formation of new hemoglobin or plasma protein or by gain in weight. The state of nitrogen balance did not alter this picture.

Unaccountable nitrogen is apparently utilized by a tissue with high nitrogen content at the expense of one with low nitrogen content. Tumor tissue (which was found to contain roughly five times as much nitrogen as fatty connective tissue) may be an example.

SUDDEN AND UNEXPECTED NATURAL DEATH

V. Causes of Death Classified by Sex and Age

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THIS IS the fifth in a series of papers on sudden and unexpected natural death and is devoted to the causes of such death at various ages. The material in question includes 2,030 persons examined at autopsy over a seven and one-half year period (Jan. 1, 1937 to June 30, 1943) in the Borough of Manhattan, New York city, by members of the Office of the Chief Medical Examiner.

As indicated in the first report [1] and in the opening paragraph of Merkel's [2] contribution, the unexpected appearance of death often outweighs its suddenness. The end may come within twenty-four hours after initial symptoms in the apparently healthy person, or there may be a quick, rapidly developing change for the worse in a gently progressive disease. It is this dramatic intrusion of the unexpected which is so often responsible for arousing suspicion of violence. A simple example is the accusation of poisoning against the husband when the wife, with whom he has often quarreled and whom he has threatened in public, is found dead after a short illness with pronounced symptoms referable to the abdomen. The neighbors are not aware that intra-abdominal hemorrhage from an oviducal pregnancy with rupture has terminated the woman's existence. On the other hand, blunt force may express itself only in internal damage so that the circumstances at the time of death may suggest a nonviolent cause. In general, it has been noted in unexpected death that the deceased had preexistent organic disease of which neither he nor his friends or relatives were aware.

The frequency of sudden and unexpected death is not known, especially since it is oftenest seen in persons who are not or have not been under medical care. Any attempt to compare it with the incidence of

From the Office of the Chief Medical Examiner, New York.

1. Helpern, M., and Rabson, S. M.: Sudden and Unexpected Natural Death: I. General Considerations and Statistics, New York State J. Med. **45**:1197-1201, 1945.

2. Merkel, H.: Plötzlicher Tod aus natürlicher Ursache, in von Neureiter, F.; Pietrusky, F., and Schütt, E.: Handwörterbuch der gerichtlichen Medizin und naturwissenschaftlichen Kriminalistik, Berlin, Julius Springer, 1940, pp. 576-589.

fatality from violence collapses when one recalls the varied lethality of the automobile in different parts of the world. Hence, it is possible only to analyze sudden and unexpected natural death and not to attempt to frame it among all types of death.

REVIEW OF PREVIOUS REPORTS

The first report [1] described the conditions under which the medical examiner functions. His chief duty is to exclude suspicion of violence; accordingly, he assumes jurisdiction over all deaths in prisons, when the person was unattended by physicians and when death was sudden and unexpected. This responsibility understandably enlarges the scope of his activities beyond those of the coroner and so furnishes a more diversified reservoir of material for study.

The Borough of Manhattan has almost 2,000,000 inhabitants (1940 census), to which are added many of the city's 500,000 daily visitors. About three fourths of the population is 21 years of age or over, and the same is probably even more true of the visitors. Over 83 per cent of all persons are white, almost 16 per cent Negro and the remainder chiefly Asiatic; interestingly enough, the three races contributed in that same proportion to the present series of 2,030 cases of sudden and unexpected natural death. The middle years of life offered more of the material in proportion to their share of the general population, the earlier years much less. Women furnished only 19 per cent of the cases studied (20 per cent of all medicolegal material), although they form 51 per cent of the population.

About 45 per cent of all deaths were due to diseases of heart and aorta, with two thirds caused by arteriosclerosis of the coronary artery. The respiratory maladies came next with nearly 23 per cent, then nervous disorders with more than 18 per cent, digestive diseases with 6.5 per cent and malaria in drug addicts with almost 3 per cent.

The second paper [3] of the series dealt with arteriosclerosis of the coronary artery, the greatest cause of sudden and unexpected natural death, resulting in 30 per cent of the 2,030 cases. It was pointed out that the diagnosis of "coronary arteriosclerosis" as a cause of death is most frequently one of exclusion, made after complete necropsy, coupled with chemical and bacteriologic studies, has ruled out other causes of death.

The third report [4] was concerned with spontaneous subarachnoid hemorrhage, which comprised one quarter of the more than 18 per cent of deaths attributed to diseases of the nervous system. In two thirds of

3. Rabson, S. M., and Helpern, M.: Sudden and Unexpected Natural Death: II. Coronary Arteriosclerosis, Am. Heart J. **35**:635-642, 1948.

4. Helpern, M., and Rabson, S. M.: Sudden and Unexpected Natural Death: III. Spontaneous Subarachnoid Hemorrhage, Am. J. M. Sc., to be published.

such deaths rupture of an aneurysm of the cerebral arterial system was discovered to be the cause of death; in most of the other cases the source of bleeding was not found. More than half the sites of rupture were in the anterior part of the circle of Willis (anterior cerebral and anterior communicating arteries; middle cerebral arteries); the right side predominated (1.4:1). It was pointed out that sometimes spontaneous subarachnoid hemorrhage may be mistaken for intracerebral or subdural bleeding because of the location of the offending aneurysm.

The fourth communication [5] described sudden and unexpected natural death in infants and young children. Such death is chiefly confined to boys and ordinarily is not encountered after the third year of life. In fact, of a group of 69 deaths in children less than 5 years old, only 6 were in children older than 2 years. Negroes are included far beyond their share of the general population; this phenomenon probably is not purely biologically racial. Almost 80 per cent of the deaths were attributed to respiratory disease. The role of the thymus is not yet clarified, and enlargement cannot be inculpated except for the rare exception. There are instances in which the lethal factor cannot be established, especially in infants 4 to 8 months old.

PRESENT STUDY

The present paper deals with the incidence of diseases making up the catalog of causes of death at various ages and in both sexes, so that a rough table of probability may be arrived at for each age group. Such a table should prove of value to those interested in legal medicine, whether their primary concern is insurance, workmen's compensation or vital statistics. Tables 1 to 3 and their graphic counterparts, figures 1 and 2, represent an analysis of the causes of death by organ systems and by half-decades of life for each sex. (Figures for 5 to 19 years of age are omitted because sudden and unexpected natural death was rare; there were only 23 deaths in all during those years.) For a better understanding of the prevalence of disease at various ages, it is useful to know the composition of the general population by age and sex. This also is recorded in figures 1 and 2 (thickness of columns).

With experience and observation a degree of accuracy may be attained by the medicolegal officer which is superficially astonishing to the inexperienced. Constant attendance at autopsies and careful review of protocols are indispensable in serving to preserve and enhance that accuracy. Before examining the various age groups, it may be well to illustrate the points just made.

5. Rabson, S. M.: Sudden and Unexpected Natural Death: IV. Sudden and Unexpected Natural Death in Infants and Young Children, J. Pediat. **34**:166-173, 1949.

TABLE 1.—*Causes of Death, by Half-Decades of Age, Among 2,030 Persons Who Died Suddenly and Unexpectedly and Were Brought to Necropsy*

Age, Yr.	Diseases of Heart and Aorta		Diseases of Respiratory Tract		Diseases of Nervous System		Diseases of Digestive Tract		Diseases of Urinary Tract		Malaria Due to Drug Addiction		Genital Causes (Female)		Miscellaneous Causes		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 5	5	9.4	36	67.9	2	3.8	5	9.4	..	....	..	....	..	....	5	9.5	53	[b]100.0
5 to 9	..	....	1	20.0	2	40.0	1	20.0	1	20.0	..	....	..	....	..	....	5	100.0
10 to 14	..	....	2	33.3	3	50.0	1	16.7	..	....	..	....	..	....	..	....	6	100.0
15 to 19	3	25.0	4	33.3	2	16.7	1	8.3	..	....	2	16.7	..	....	..	....	12	100.0
20 to 24	7	14.6	4	8.3	8	37.5	6	12.5	2	4.2	4	8.3	4	8.3	3	6.3	48	100.0
25 to 29	13	15.7	18	21.7	29	34.9	8	9.6	1	1.2	4	4.9	9	10.8	1	1.2	83	100.0
30 to 34	34	26.8	35	27.6	32	25.2	4	3.1	3	2.4	10	7.9	7	5.5	2	1.5	127	100.0
35 to 39	62	36.3	44	25.8	40	23.3	10	5.8	5	2.9	7	4.1	3	1.8	..	....	171	100.0
40 to 44	96	38.6	57	22.9	53	21.3	16	6.4	7	2.8	14	5.6	3	1.2	4	1.6	250	100.0
45 to 49	134	44.5	61	20.3	65	21.6	23	7.6	4	1.3	9	3.0	..	....	5	1.7	301	100.0
50 to 54	167	53.3	64	20.7	47	15.2	22	7.1	5	1.6	4	1.3	..	....	1	0.3	310	100.0
55 to 59	134	58.1	49	21.2	27	11.7	16	6.9	3	1.3	1	0.4	..	....	1	0.4	231	100.0
60 to 64	116	59.1	35	17.9	26	13.3	4	2.0	5	2.6	..	....	..	....	10	6.1	196	100.0
65 to 69	70	54.7	26	20.3	16	12.5	6	4.7	2	1.6	..	....	..	....	8	6.2	128	100.0
70 to 74	36	55.4	11	16.9	5	7.7	6	9.1	1	1.8	..	....	..	....	5	9.1	64	100.0
> 75	18	40.3	13	28.8	6	13.3	2	4.4	2	4.4	..	....	..	....	4	8.8	45	100.0
Total	895	44.1	460	22.7	373	18.4	131	6.4	41	2.0	55	2.7	26	1.3	49	2.4	2,030	100.0

TABLE 2.—*Causes of Sudden and Unexpected Natural Death Among 1,610 Men, by Half-Decades of Age*

Age, Yr.	Diseases of Heart and Aorta		Diseases of Respiratory Tract		Diseases of Nervous System		Diseases of Digestive Tract		Diseases of Urinary Tract		Malaria Due to Drug Addiction		Miscellaneous Causes		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 5	1	2.3	33	75.0	2	4.5	3	6.8	..	....	..	....	5	11.4	44	100.0
20 to 24	5	21.7	2	8.7	9	39.1	..	....	1	4.5	3	13.0	3	13.0	23	100.0
25 to 29	7	20.0	10	28.6	14	40.0	..	....	..	....	4	11.4	..	....	35	100.0
30 to 34	31	35.6	22	25.3	20	23.0	2	2.3	1	1.2	9	10.3	2	2.3	87	100.0
35 to 39	56	42.0	34	25.6	31	23.3	3	2.3	3	2.3	6	4.5	..	....	133	100.0
40 to 44	88	44.6	44	22.2	41	20.7	8	4.0	5	2.5	12	6.0	..	....	198	100.0
45 to 49	130	49.0	49	18.3	57	21.3	18	6.7	2	0.7	9	3.3	2	0.7	267	100.0
50 to 54	153	56.7	57	20.6	34	12.5	20	7.3	4	1.0	4	1.5	..	....	272	100.0
55 to 59	122	62.6	38	19.5	19	9.7	13	6.7	2	1.0	1	0.5	..	....	195	100.0
60 to 64	102	61.5	31	18.7	19	11.4	3	1.8	3	1.8	..	....	8	4.8	166	100.0
65 to 69	65	61.9	19	18.1	14	13.3	3	2.9	1	0.9	..	....	3	2.9	105	100.0
70 to 74	31	63.3	10	20.4	4	8.2	1	2.0	1	2.0	..	....	2	4.1	49	100.0
> 75	15	42.3	9	24.4	6	16.6	1	2.8	2	5.6	..	....	3	8.3	36	100.0
Total	806	50.1	358	22.2	270	16.8	75	4.7	25	1.6	48	2.9	28	1.7	1,610	100.0

TABLE 3.—*Causes of Sudden and Unexpected Natural Death Among 397 Women, by Half-Decades of Age*

Age, Yr.	Diseases of Heart and Aorta		Diseases of Respiratory Tract		Diseases of Nervous System		Diseases of Digestive Tract		Diseases of Urinary Tract		Malaria Due to Drug Addiction		Genital Causes (Female)		Miscellaneous Causes		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
< 5	4	45.5	3	33.3	..	....	2	22.2	..	....	..	....	..	....	..	....	9	100.0
20 to 24	2	8.0	2	8.0	9	36.0	6	24.0	1	4.0	1	4.0	4	16.0	..	....	25	100.0
25 to 29	6	12.5	8	16.7	15	31.3	8	16.7	1	2.0	..	....	9	18.8	1	2.0	48	100.0
30 to 34	3	7.5	12	30.0	13	32.5	2	5.0	2	5.0	1	2.5	7	17.5	..	....	40	100.0
35 to 39	6	16.0	10	26.8	9	23.0	7	18.4	2	5.3	1	2.6	3	7.9	..	....	38	100.0
40 to 44	7	13.7	13	25.6	12	23.5	8	15.7	2	3.9	2	3.9	3	5.9	4	7.8	51	100.0
45 to 49	4	11.8	12	35.3	8	23.5	5	14.7	2	5.9	..	....	..	....	3	8.8	34	100.0
50 to 54	14	36.9	7	18.4	13	34.2	2	5.3	1	2.6	..	....	..	....	1	2.6	38	100.0
55 to 59	12	33.3	11	30.6	8	22.2	3	8.3	1	2.8	..	....	..	....	1	2.8	36	100.0
60 to 64	14	47.2	4	13.2	7	23.1	1	3.3	2	6.6	..	....	..	....	2	6.6	30	100.0
65 to 69	5	21.7	7	30.5	2	8.7	3	13.0	1	4.4	..	....	..	....	5	21.7	23	100.0
70 to 74	6	37.6	1	6.2	1	6.2	5	31.2	..	....	..	....	..	....	3	18.8	16	100.0
> 75	3	33.3	4	44.5	..	....	1	11.1	..	....	..	....	..	....	1	11.1	9	100.0
Total	86	21.7	94	23.7	97	24.5	53	13.4	15	3.8	5	1.3	26	6.5	21	5.1	397	100.0

A 52 year old printer was found dead on the stairs of his place of work early in the afternoon. A few minutes before his body was discovered, head down, close to the landing of the floor below, he had been seen talking with the foreman of the shop; he was apparently in good health. When the body was examined by a medical examiner almost two hours later, it was still warm. The face was slightly cyanotic. There were no injuries noted on the head, trunk or limbs. Someone at the scene remarked that the dead man had been at home for several days the previous week and that he "had been taking pills." There was no suspicion of violence, and the examiner diagnosed the cause of death as "coronary artery sclerosis." The body

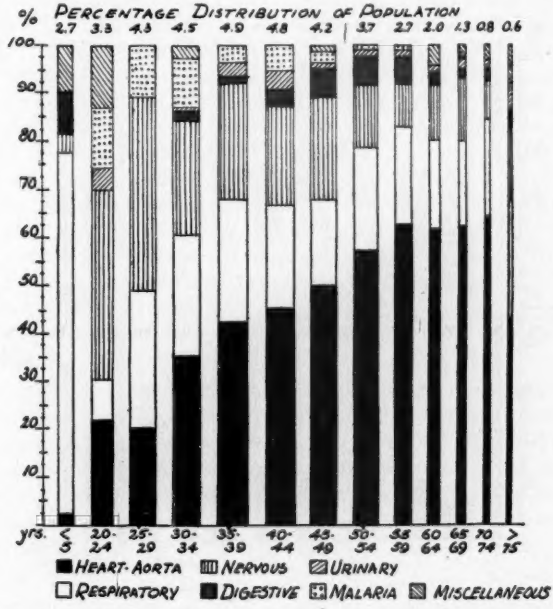

Fig. 1.—Graphic representation of causes of sudden and unexpected natural death, by half-decades of age, among 1,610 men, verified by necropsy observation.

was removed for the convenience of the workmen to the city morgue, where it was claimed by the widow and then cremated.

Later, the widow asserted that her husband had not died of natural causes and that the cause of death was a blow to the head sustained while her husband was working on a printing press the day before he died. She described a large laceration behind one ear which she allegedly dressed when he arrived home from his place of employment. A fellow worker recalled that the deceased had said he had struck his head, and another that he had seen a bloody handkerchief in his hand, but no one had examined the head or noted any bleeding from it. The medical examiner testified that he had run his fingers through the hair and over the scalp of the dead man but neither saw nor felt any laceration or blood.

A physician who appeared for the claimant asserted that, in his opinion, the deceased had died of subdural hemorrhage provoked by the blow on the head the day before death. He also rejected the diagnosis of coronary artery sclerosis because, according to the widow, her husband had never complained of symptoms referable to the heart.

The medical examiner, in his testimony, pointed out that sudden and unexpected death from coronary artery disease may be preceded either by no symptoms or by manifestations so slight or altered as not to cause the person to visit a physician or complain to friends or relatives. In short, a clinical history is not essential in arriving at a cause of death, helpful as it is. He further showed that more than

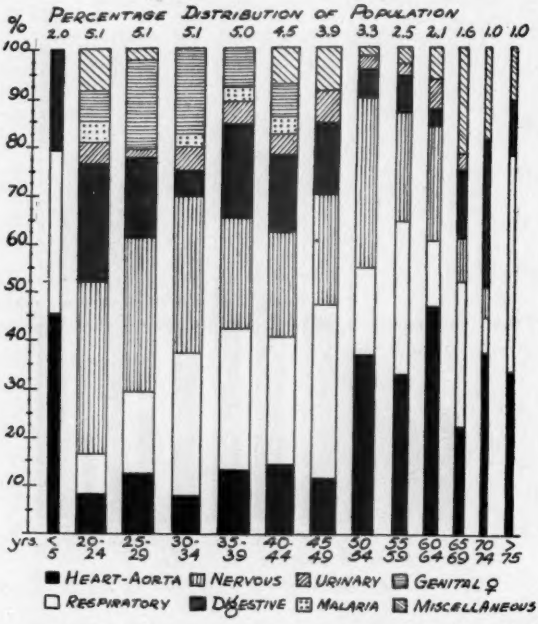

Fig. 2.—Graphic representation of causes of sudden and unexpected natural death, by half-decades of age, among 397 women, verified by necropsy observation.

53 per cent of men and women between 50 and 54 years of age die of diseases of the heart and aorta, that the overwhelming majority of these deaths is caused by coronary artery sclerosis and that white men make up 90 per cent of all deaths due to disease of the coronary artery. Other causes of death were to be considered, it was true, but the weight of probability rested with coronary artery sclerosis.

The denouement came several months later when a chart bearing the deceased's name was found in the files of a large municipal hospital. Beginning two years before his death, he had paid many visits to the outpatient department because of pain in the substernal region and left arm, dyspnea and collapse while walking. Electrocardiographic changes suggested the presence of myocardial disease.

DEATHS BY AGE GROUPS

Early Years of Life.—There were 53 deaths in children younger than 5 years of age, or 2.6 per cent of the total of 2,030 cases; most of these children were but a few months old. Two thirds of them died of respiratory disease, almost without exception of bronchitis or bronchopneumonia. The pediatrician is aware of the insidious progress of pulmonary infection in the infant, although the nonspecialist is less well acquainted with it. With a slight cough, little or no fever, a lively disposition and no great impairment of appetite, the baby is not regarded as gravely ill. The next morning it is found dead in its crib or carriage. Such is the story among both rich and poor. Too often the authorities are prone to forget respiratory disease in these circumstances, especially when the infant is found face down on the pillow or overlain by a bed partner, either a parent or another child of the family. It is easier to attribute death to suffocation by neglect or by purpose. The obvious conditions surrounding death in such circumstances should prompt more than ever the performance of a necropsy. Next, the pulmonary findings at autopsy must be interpreted in the light of the dead child's age, physical status and the conditions under which death occurred. Bacteriologic studies are most helpful, both in the evaluation of the individual case and in their epidemiologic implications. It must not be overlooked, however, that between the ages of 3 and 10 months there may not be a demonstrable cause of death.

The death rates for digestive maladies and disturbances of heart and aorta followed that for respiratory disease, with less than 10 per cent caused by each. Acute appendicitis still claimed its victims, as did acute intussusception. Congenital cardiac anomalies were also as frequent or infrequent. It is of interest to record that acute meningitis is apparently rarely a cause of sudden and unexpected natural death in infants and young children.

When the data are arranged for each sex, striking differences are noted (tables 2 and 3; figs. 1 and 2). Bronchitis and bronchopneumonia were 2.5 times as common among male babies as among female infants. This sharp contrast may be in part responsible for the change in the sex distribution of the population in the next half-decade (5 to 9 years). Whereas 2.7 per cent of the general population in 1940 consisted of boys under 5 years of age, and only 2.0 per cent of girls, the percentages were the same for the next half-decade (2.6 per cent). Digestive disturbances as a cause of death were twice as frequent in girls as compared with boys, and diseases of the heart and aorta were four times as common in girls as in boys. Only in this single half-decade of life was there more cardiovascular disease among girls than among boys, a striking but perhaps insignificant exception. The single case among the boys

was one of congenital cardiac anomaly; in the opposite sex, there were 2 such cases, in addition to 1 each of neoplasm of the heart and acute suppurative pericarditis.

5 to 9 Years.—The second half of the first decade of life was almost free of sudden and unexpected natural death; only 5 deaths were recorded in this age group.

10 to 14 Years.—Here, too, sudden and unexpected death was rare (6 cases).

15 to 19 Years.—During this period sudden natural death was apparently twice as common as in the preceding half-decade, although only 10 per cent more of the total population is in this group. The number of deaths, 12, was small, and no valid conclusions can be drawn.

20 to 24 Years.—This half-decade showed fewer deaths (48) than the first 5 years of life (53), even though it has almost twice as many members among the total population. Accordingly, sudden and unexpected natural death was half as common at this age as shortly after birth. Here, in early young adulthood, there was a greater diversification in the causes of death, with each cause offering a proportionately smaller contribution. Over one third of the deaths was from nervous disorders (meningitis, spontaneous subarachnoid hemorrhage, cerebral hemorrhage and cerebellar hemorrhage, in descending order of frequency), equally divided between the sexes. More than 14 per cent of the persons succumbed to diseases of the heart and aorta, half of whom (3 persons) had coronary arteriosclerosis. The latter malady made its first appearance in this age group, to enter a greater and greater claim with each advancing year. Tubal pregnancy with rupture caused 4 deaths. This represents 8.3 per cent of the total for both sexes, but 16 per cent of the total female deaths (25). Among the other causes of death, the sexes were about equally represented, except for coronary artery disease. The deaths from respiratory disease and malaria in drug addicts were equal in number, 4, or 8.3 per cent; the latter occurred twice as frequently in men, whereas the incidence of the former was the same in both sexes.

25 to 29 Years.—This half-decade offered the first prominent contribution to sudden and unexpected natural death with 83 cases; this figure represented, however, only 4 per cent of the 2,030 cases, although persons in these years comprise more than 9 per cent of the total population. Here, as in the previous period, one third of the deaths was due to diseases of the nervous system, with fewer fatalities from meningitis and more from spontaneous subarachnoid hemorrhage. More than 21 per cent of the deaths were from disease of the respiratory system, chiefly pneumonia and pulmonary tuberculosis, in descending order of frequency. Disturbances of heart and aorta claimed over 15 per cent (coronary arteriosclerosis, syphilitic aortitis and subacute

bacterial endocarditis, mainly). Bacterial endocarditis is ordinarily considered a disease of pronounced, if not always protracted, symptoms. There are enough samples in this series to indicate that such is not always the case.

A young man employed as a stock clerk in a large department store remained home from work because of general malaise. At noon on the second day of his stay at home, he was removed to a hospital by ambulance. He had a mild fever and rales at both pulmonary bases. Death took place four hours later. At autopsy, there was acute passive congestion of the lungs and abdominal viscera. Acute ulcerative endocarditis of the aortic valve was observed which had caused incompetency. Bacterial staining of the valvular lesion showed gram-positive diplococci, suggesting pneumococci.

Digestive disorders and tubal abortion each caused about 10 per cent of the total of 83 deaths. The former category included pylephlebitis with hepatic abscess, bleeding esophageal varices, and acute appendicitis. Ruptured ectopic pregnancy represented almost 19 per cent of the female deaths (the total was 48). Malaria acquired during drug addiction accounted for 5 per cent of the deaths.

At this point it may be well to discuss briefly the problem of malaria and its relation to drug addiction. The importation of malarial plasmodia into the community by casualties returning from various war theaters has enlarged the reservoir for potential spread. The spread may occur in two ways, either by mosquito (anopheline mosquitoes are found in various parts of the United States) or through artificial inoculation by hypodermic needle during illicit administration of opiates. It is unfortunate that some patients may become drug addicts because of the necessity of using opiates to relieve the pain or discomfort of chronic maladies. The difficulties, both technical and economic, in securing the drugs have prompted and will prompt sufferers to pool their resources and use a common needle and syringe or syringe substitute. In this way malaria has been spread in communities with often epidemic-like character and with a high fatality rate. The presence of pitting scars on thighs and forearms should be a reminder to consider malaria, usually of the estivoautumnal type, as a possible cause of sudden and unexpected natural death.

An analysis of the age group between 25 and 29 years by sex indicates that deaths due to diseases of heart and aorta were one and a half times as common in men as in women; the same is true of death caused by respiratory illnesses, but the proportion was somewhat less for nervous maladies. Deaths from digestive disorders were exclusively among women, whereas the reverse was noted for malaria. The urinary apparatus furnished but a single case, the death resulting from malignant nephrosclerosis in a woman.

30 to 34 Years.—Beginning with this half-decade, death from diseases of the heart and aorta moved into a more prominent position, slightly outnumbered by those due to respiratory conditions it is true, but hereafter to lead in ever more striking fashion. Almost 27 per cent of the deaths were attributed to cardiovascular diseases, with male outnumbering female deaths by virtually 5 to 1; there were only 3 among the women. Among the men coronary arteriosclerosis predominated over other aortic and cardiac lesions (5:4).

Death caused by disorders of the respiratory apparatus was first with slightly less than 28 per cent (25.3 per cent among men; 30.0 per cent among women). The men had 7 deaths from pulmonary tuberculosis and 10 from pneumonia; for women the figures were 4 and 4.

In third place were deaths from disease of the nervous system (25.2 per cent), with female deaths leading, 4 to 3. There were 10 deaths from spontaneous subarachnoid hemorrhage among men and 7 among women; it should not be forgotten, however, that in both necropsied and nonnecropsied cases from the Office of the Medical Examiner only 20 per cent of the material is furnished by women. Death from digestive disorders, although not common, was twice as frequent in women. Death due to malaria, taking place almost exclusively in men, totaled almost 8 per cent among both sexes and 10.3 per cent among men. Tubal pregnancy with rupture, resulting in 5.5 per cent of the deaths in this half-decade, accounted for 17.5 per cent of the female fatalities. Death from urinary tract disorders (totaling 2.4 per cent) occurred in 5 per cent of women and 1.2 per cent of men.

35 to 39 Years.—Disease of heart and aorta came into first place as a cause of sudden and unexpected natural death with 36.3 per cent (men 42 per cent; women 16 per cent). In this category the cause of 37 of the 56 deaths was diagnosed as coronary arteriosclerosis and that of 8 as syphilitic aortitis. Four of the 6 deaths in women were caused by the latter disease. A little more than a quarter of the deaths was provoked by respiratory ailments; that same proportion held for each sex. There were 13 deaths from lobar pneumonia in men, for example, but only 1 in women; 9 in men from pulmonary tuberculosis, as compared with 2 in women, and 3 in men from nontraumatic pulmonary embolism or infarction contrasted with 1 in a woman.

The rate for disturbances of the nervous system was third, 23.3 per cent (men 23.3 per cent; women 23 per cent). Although the position held in both sexes was relatively the same, the distribution of the individual diseases in this category differed. Whereas two thirds of the men died from some form of intracranial hemorrhage, only one third of the 9 women died from this. Two women, but no men, died

of suppurative meningitis. There were 2 men and 1 woman in the group with primary brain tumor and 1 woman with secondary neoplasm of the brain.

Fourth in the half-decade between 35 and 39 years were deaths due to maladies of the digestive apparatus (5.8 per cent); numerically, 3 men and 7 women died from this cause, but on the basis of percentage, 2.3 per cent and 18.4 per cent, respectively. The men died of hemorrhage (esophageal varices, 2; omental varices, 1). Two women died of some form of bacterial enteritis and an equal number of intestinal obstruction due to postoperative adhesions.

Next in order of frequency was death from malaria in drug addicts (4.1 per cent), with 6 men (4.5 per cent) and 1 woman (2.6 per cent), followed by that due to urinary tract disorders (2.9 per cent). Tubal abortion accounted for almost 8 per cent of deaths among women in this age group but dwindled to 1.8 per cent for the entire group.

40 to 44 Years.—This period of life, too, was marked by the steplike increase in sudden and unexpected death due to cardiac and aortic diseases (38.6 per cent). The role of these disorders is more apparent when it is noted that they accounted for 44.6 per cent of deaths in men and for only 13.7 per cent in women. Of the 7 female deaths, the cause in 5 was diagnosed as syphilic aortitis. Among the 88 men, 59, or two thirds, came to their end because of coronary arteriosclerosis.

Compared with the heart and aorta, deaths from disorders of the other organ systems lagged far behind. The deaths caused by disease of the respiratory and nervous systems came next, with only 22.9 and 21.3 per cent, respectively. Analyzed by sex, the rates were 22.2 per cent for men and 25.6 per cent for women for the first and 20.7 and 23.5 per cent for the second system. Of the 44 men who died from diseases of the respiratory tract, 20, or almost half, died of lobar pneumonia, compared with one third of the 13 women. Bronchopneumonia claimed 6 men and 7 women, while embolism or infarction took 7 men and no women.

Half the 41 men whose death resulted from disorders of the nervous system died of intracranial bleeding, 8 of them from spontaneous subarachnoid hemorrhage; exactly half the 12 women died from the latter disorder. Six men, but no women, received the terminal diagnosis of cerebral infarction (embolism or thrombosis), while deaths of 5 men and no women were classified as due to suppurative meningitis. There were 4 men and 2 women with primary brain tumor.

Only one sixteenth of the deaths in this age group (40 to 44 years) was in the category of digestive tract maladies, 15.7 per cent in women and 4.0 per cent in men, with 8 deaths for each. Among the women,

there were 2 subjects with abdominal neoplasms and an equal number with intestinal obstruction caused by lymphopathia venereum (lymphogranuloma venereum).

Almost 6 per cent of the series died from malaria acquired during drug addiction; there were 12 men (6.0 per cent) and 2 women (3.9 per cent). Slightly less than 6 per cent of the women succumbed to tubal abortion with hemorrhage, a condition accounting for only 1.2 per cent of the total in this period of life. There was but a small group of deaths due to urinary tract ailments, forming only 2.8 per cent (2.5 per cent male; 3.9 per cent female).

45 to 49 Years.—Still climbing, diseases of heart and aorta claimed 44.5 per cent of the victims of sudden and unexpected natural death, 49 per cent of the men and 11.8 per cent of the women. As prominent as heretofore, coronary arteriosclerosis killed 89 of the 130 men, with only a single Negro and no women represented. Again, the rate for deaths from respiratory and nervous disorders lagged, each causing less than half that of the cardioaortic category. The first group had 20.3 per cent deaths (18.3 per cent male and 35.3 per cent female). Thirty of the 49 men had lobar pneumonia, 9 pulmonary tuberculosis and 5 bronchopneumonia; for the 10 women, the figures were 2, 1 and 7, respectively.

Deaths due to nervous system maladies (21.6 per cent) were distributed as follows: 21.3 per cent male and 23.5 per cent female (8 cases). Cerebral hemorrhage accounted for 22 of the 57 deaths among men in this classification and spontaneous subarachnoid bleeding for 7. Six men, but no women, had primary intracranial tumors; 4 men died of suppurative meningitis. Digestive disorders made up 7.6 per cent of the deaths, with 6.7 per cent in the men (18) and 14.7 per cent in the women (5). Perforated peptic ulcer was the diagnosis for 4 men; 2 of each sex died of cirrhosis of the liver, and 2 men died from strangulated hernia, while 4 men succumbed to acute hemorrhagic pancreatic necrosis.

There were no deaths from ruptured tubal pregnancy and 9 (3 per cent) from malaria, all among men (3.3 per cent). In this half-decade (45 to 49 years) fatalities from urinary tract disturbances were among the lowest (1.3 per cent) recorded for any age group, with 2 deaths (0.7 per cent) among the men and 2 (5.9 per cent) among the women.

50 to 54 Years.—The percentage due to disorders of the heart and aorta continued to rise, causing 53.3 per cent of all sudden and unexpected natural deaths. In this group also such diseases assumed and held a more prominent role among women, the percentage being 36.9, as compared with 11.8 per cent in the preceding half-decade; for men the rate was 56.7 per cent. Of the 153 men, 127, or four fifths, died of coronary arteriosclerosis; the same cause accounted for more than

half (8) the 14 female deaths. Three women died of spontaneous aortic rupture with intrapericardial hemorrhage and an equal number of cardivalvular defects. Syphilis of the aorta was the diagnosis on death for 15 men and valvular disturbances for 10 men.

Deaths caused by respiratory diseases came in a distant second with 20.7 per cent (20.6 per cent male; 18.4 per cent female). Thirty-two, or more than half the 57 men, had lobar pneumonia and 9 each had bronchopneumonia and tuberculosis: among the 7 women the figures were 3, 3 and 6

Third in frequency were deaths due to maladies of the nervous system (15.2 per cent), with 12.5 per cent (34) among men and 34.2 per cent (13) among women. Intracranial hemorrhage was most prominent, claiming 20 men, including 12 who died from intracerebral hemorrhage and 6 from spontaneous subarachnoid hemorrhage; there were 10 women (7.3 per cent). Primary brain tumor was diagnosed in 7 instances (in 4 men and 3 women).

The next most commonly involved organ system was the digestive, causing 7.1 per cent of deaths (7.3 per cent male; 5.3 per cent female). Five of the 20 men succumbed to hemorrhage from esophageal varices, 3 to hepatic cirrhosis, 2 to acute hemorrhagic pancreatic necrosis and 2 to perforation of an esophageal tumor into the aorta. There were but 2 women in this age group. Urinary diseases and malaria played but an insignificant role in deaths in either sex.

55 to 59 Years.—Cardioaortic disorders approached the peak, to be reached in the next half-decade by a small and insignificant step. Of deaths 58.1 per cent were caused by these disorders, 62.6 per cent among the men and 33.3 per cent among the women. Death in 93, or three fourths, of the 122 men, and in 8, or two thirds, of the 12 women, was classified as caused by coronary arteriosclerosis. Cardivalvular incompetency claimed 14 men and syphilitic aortitis 6.

Deaths resulting from disease of the respiratory tract continued to hold second place, with 21.2 per cent (19.5 per cent in men; 30.6 per cent in women). Of the 38 men, 21 had lobar pneumonia, 6 bronchopneumonia and 6 pulmonary tuberculosis; among the 11 women, the figures were 1, 8 and 1, respectively. Trailing farther behind with 11.7 per cent were deaths from nervous system causes. There were 9.7 per cent (19) for the men and 22.2 per cent (8) for the women. Deaths from cerebral hemorrhage accounted for 7 men and 3 women, pontile bleeding for 2 and 0, spontaneous subarachnoid hemorrhage for 2 and 2 and primary intracranial tumor for 1 and 1.

Diseases of the digestive apparatus were a poor fourth (6.9 per cent). Of the patients 13 were men (6.7 per cent) and 3 women (8.3 per cent). Of the men, 4 died of cirrhosis of the liver and 3 of acute hemorrhagic

pancreatic necrosis. Here, too, deaths caused by disease of the urinary tract had no important part to play.

60 to 64 Years.—The death rate for diseases of the heart and aorta was at its zenith (59.1 per cent) in this age group. Among the men (61.5 per cent) the maximum was to be reached in another decade; here, however, the rate for women (47.2 per cent) was at the peak. Coronary artery disease was the diagnosis in 74, or almost three fourths, of the 102 male deaths and in 11, or four fifths, of the 14 female deaths. Seven men died of cardiovalvular lesions, 12 of syphilis of the aorta and 3 of generalized arteriosclerosis.

Lagging more than ever behind in second rank was the incidence of death due to diseases of the respiratory tract (17.9 per cent). There were 31 men (18.7 per cent) and 4 women (13.2 per cent). Eighteen men and 2 women had lobar pneumonia, 5 and 1 bronchopneumonia, 2 and 1 pulmonary embolism or infarction and 2 men abscess of the lung.

Third in order of frequency were deaths caused by disturbances of the nervous system (13.3 per cent), with 19 men (11.4 per cent) and 7 women (23.1 per cent). Eight men had the diagnosis of cerebral hemorrhage, 2 of spontaneous subarachnoid hemorrhage, 3 of nonepidemic meningitis and 2 of arteriosclerotic softening of the brain; the figures for women were 2, 2, 2 and 1, respectively. Lesions of the digestive tract were seen only 4 and those of the urinary apparatus 5 times.

65 to 69 Years.—During this half-decade there was a drop in the percentage of sudden and unexpected natural deaths due to cardioaortic lesions for the sexes taken together; the rate for men did not reach the peak until 70 to 74 years of age. The total was 54.7 per cent, divided into 61.9 per cent (65 deaths) among the men and 21.7 per cent (5) among the women. Fifty, or three fourths of the men and 3, or three fifths of the women died of coronary arteriosclerosis.

In the field of death resulting from diseases of the respiratory system (20.3 per cent), there were 19 men (18.1 per cent) and 7 (30.5 per cent) women. Eight deaths among the men and 1 among the women were caused by lobar pneumonia, 4 and 3 by bronchopneumonia, 1 and 1 by pulmonary embolism or infarction and 4 and 0 by tuberculosis of the lungs.

The disorders of the nervous system held third place with 12.5 per cent of the deaths. Of the patients only 2 were women (8.7 per cent) and 14 men (13.3 per cent). Of the latter, 3 had cerebellar, 6 cerebral and 1 spontaneous subarachnoid hemorrhage, and 2 had cerebral arterial thrombosis with infarction. There were 3 deaths from lesions of the digestive apparatus in each sex and 1 in each from urinary system maladies.

70 to 74 Years.—Although the group of disturbances of heart and aorta accounted for 55.4 per cent of deaths in both sexes, it covered 63.3 per cent (31 deaths) among the men at this age, the highest sex percentage for any organ system in the entire study. Among the men, 24, or three fourths, succumbed to coronary arteriosclerosis; 4 of the 6 women died of similar cause. Almost 17 per cent of deaths were due to respiratory lesions; only 1 occurred in a woman. Of the 10 men (20.4 per cent) 3 had lobar pneumonia, 2 bronchopneumonia and 2 pulmonary tuberculosis.

In third place came deaths due to digestive disorders (9.1 per cent), with 5 in the women (31.2 per cent) and 1 in men (2.0 per cent). In the former sex the diagnoses were gastric carcinoma, intra-abdominal hemorrhage from neoplastic perforation, strangulated hernia, intestinal obstruction caused by new growth and peritonitis from neoplastic perforation of the intestine.

75 Years and Older.—Except for the years between 5 and 19 with their total of 23 deaths, this period of life had, understandably, the fewest number (45) in this study. Eighteen (40.3 per cent) persons had cardioaortic maladies, of which 42.3 per cent (15) were men and 33.3 per cent (3) women. Of the men 11 suffered from coronary sclerosis; the same diagnosis was made for 1 of the women. The respiratory system was next with 28.8 per cent (13 deaths), with 24.4 per cent (9) in men and 44.5 per cent (4) in women. One man and 2 women had lobar pneumonia, 2 and 2 bronchopneumonia and 4 and 0 bronchopneumonia with generalized arteriosclerosis. There were 6 deaths (13.3 per cent) from nervous tract lesions, all in men, and 2 (4.4 per cent) each from digestive and urinary disorders.

SUMMARY AND CONCLUSIONS

Two thousand and thirty cases of sudden and unexpected natural death in which autopsy was performed are analyzed to show the incidence of the various causes of death in successive half-decades of life. Based on this analysis, the expectancy of the various causes of death for any age group is recorded. This should prove of worth in the evaluation of fetal factors by those interested in legal medicine. The information should also be of value in emphasizing the trend of natural diseases at various ages. This assists in the recognition of unsuspected diseases, including those which are infectious and, therefore, a matter of concern to the public health, as well as to the individual welfare. In this respect, it is interesting to point out the relatively frequent incidence of death from active pulmonary tuberculosis in persons of the older age groups, beginning in middle age. This contrasts sharply with the usual failure to suspect the condition at this time of life.

HEPATIC INSUFFICIENCY AND CIRRHOSIS IN DIABETES MELLITUS

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CONTRARY to general belief, there appears to be a paucity of clinical studies on the pathologic effect of diabetes mellitus on the cellular structure and function of the liver. It is through the fine work and attractive theories of Soskin that the spotlight of diabetic investigation has again found the liver. This organ, with its multiplicity of function, is gradually emerging from a veil of mystery that has long surrounded it and is being forced to reveal its secrets through the careful and persevering study of the biochemist, physiologist and pathologist and, by means of their efforts, to the clinician.

If, as Soskin and Levine [1] suggested, the liver is the regulatory organ, the thermostat in determining the blood level of glucose, does hepatic dysfunction disrupt this fine balance and act to produce abnormalities of glycemia, or, on the other hand, do wide sweeps in diabetic control result in disturbance of hepatic function? The lability of hepatic glycogen and the decrease to absence observed in either hypoglycemia or hyperglycemia are well known. The processes of gluconeogenesis, glycogenesis and glycogenolysis are familiar to any student of diabetes. It seems quite apparent, then, that the liver in the diabetic patient must do much more work in its attempt to maintain the health of the organism than would be expected of that organ in a normal person. Does this added labor result in damage to the liver?

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REVIEW OF LITERATURE

Dragsted [2] demonstrated the effect of pancreatectomy in dogs on hepatic fat infiltration and the lipotrophic action of pancreatic extract. This same lipotrophic effect has, of course, been observed to occur with several substances, the basis of which appears to be choline. Marble and his associates [3] described the enlarged liver seen in juvenile diabetic patients and ascribed it to this fatty infiltration. The fatty liver of the person with diabetes is referred to in many textbooks; one is almost led to believe that fatty liver is the rule in these patients. Conner [4] has presented evidence in alcoholic patients which indicates that fatty infiltration precedes the diffuse fibrosis of the liver and the latter is a sequel to the fatty infiltration. The Gillmans,[5] by means of multiple liver biopsies on natives of South Africa, were able to trace the effects on the liver of nutritional deficiencies, from fatty infiltration through to diffuse hepatic fibrosis. Himsworth [6] stated: "There can then be no doubt that in man, as in experimental animals, heavy, prolonged, fatty infiltration of the liver can lead to diffuse hepatic fibrosis." If heavy fatty infiltration of the liver is common in diabetes, then one would expect a high incidence of cirrhosis and hepatic dysfunction in diabetic persons.

Total hepatectomy can be expected to bring out most strikingly the part played by the liver in blood sugar regulation. Mann and McGrath,[7] working with dogs, have shown the consistent hypoglycemic effect of this procedure, the animals progressing to hypoglycemia, convulsions and coma and death in several hours. In the consideration of human material there have been reports of carcinomatous and toxic destruction of the

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liver, with resultant severe hypoglycemia, when carbohydrate was withheld. Conn and his co-workers [8] reported hypoglycemia resulting from infectious hepatitis; studies revealed a normal respiratory quotient, which they considered to rule out hyperinsulinism as the etiologic factor. Nadler and Wolfer [9] reported on a patient having primary liver cell carcinoma with hypoglycemia, requiring glucose feedings. This case had another interesting feature in that there were no prominent symptoms of hepatic failure other than the lowered blood sugar level. A similar case was reported by Crawford [10] and another by Elliot.[11] Cross and Blackford [12] described a patient with fatal neoarsphenamine poisoning in whom hypoglycemia was a prominent factor and autopsy revealed severe hepatic damage. Hypoglycemia from hepatic damage by phosphorus was also reported.

Let us now examine the ledger for information concerning the other side of the picture, namely, hyperglycemia related to hepatic damage. Here we do not find the information as plentiful. Soskin and his collaborators [13] demonstrated that a normal dextrose tolerance curve could be obtained in depancreatized dogs which were receiving a constant injection of insulin and dextrose just sufficient to maintain the blood sugar at a constant level. When a dog was hepatectomized and given a constant injection of dextrose just sufficient to maintain the blood sugar at a constant level, the animal consistently yielded "diabetic" dextrose tolerance curves.

Althausen and Thoenes,[14] studying rabbits after phosphorus had been given as the hepatotoxic agent, stated:

> The first functional deficiency of the liver to appear was a failure on the part of this organ to maintain the normal blood sugar level. Later, a progressive decrease in sugar tolerance was manifested which could be explained at least in part by lack of glycogen deposition in the liver following the administration of dextrose, water and insulin. In the last stages of poisoning after the modified dextrose tolerance test blood sugar curves ending in hypoglycemia were typical.

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Decreased dextrose tolerance in the presence of infectious diseases has been reported frequently. Williams and Dick [15] substantiated this observation in animal and human subjects. Glycosuria and lower carbohydrate tolerance were noted in 41 per cent of their patients with acute infectious diseases. Sweeney and his associates [16] reported that experimental toxemia in rabbits produced by poisoning with diphtheria toxin resulted in decreased dextrose tolerance. Soskin and his co-workers,[17] using diphtheria toxin on depancreatized dogs, encountered the same decreased dextrose tolerance and ascribed it to interference with hepatic function. Newburgh and Conn [18] reported on 35 obese patients having diabetic dextrose tolerance curves and clinical diabetes in whom carbohydrate metabolism was restored to normal when weight was reduced to a standard level and remained at this level for the two year period of observation. They suggested fatty infiltration of the liver with hepatic dysfunction as the responsible factor.

Lichtman [19] cited Hetenyi as unable to demonstrate any particular change in fasting blood sugar levels in patients with various hepatic diseases, while Isaacs demonstrated a hyperglycemic curve which was often higher and more protracted than in normal persons. Lazner and his associates,[20] in their investigation of the intravenous dextrose tolerance test, used this procedure on 7 patients with hepatic disease and obtained three normal and three moderately elevated curves, with one moderately depressed. Campbell and Tagnon [21] used the same test on 25 patients with hepatic disease and noted a normal dextrose tolerance curve in the greater percentage of them. Soskin [22] recorded a greater hyperglycemic peak than normal in persons with disease of the liver, but without exception there would be a return to the normal level within one hundred and twenty minutes.

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Hyperglycemia associated with biliary tract disease has been described, but it was Lande and Pollack in 1935 [23] who suggested the possibility of hepatic damage as the cause. They cited 3 cases of patients with biliary tract obstruction with hyperglycemia requiring insulin. In all 3 the carbohydrate tolerance returned to normal after the obstruction was removed. Leevy and his co-workers [24] recently reported transient diabetic-like states, in which the dextrose tolerance returned to normal after hepatic therapy.

We now turn to the question of hepatic function in diabetes and the effects of diabetic control. Here we have little material and that quite conflicting, since the observations were based on use of the laboratory tests available at the time.

Meyer [25] in 1931 observed hepatic dysfunction to be present in 28 per cent of 100 diabetic patients. It was his opinion that the longer the diabetic condition remained uncontrolled the more frequently hepatic dysfunction became demonstrable. Wilder [26] stated that at the Mayo Clinic between 1935 and 1937 no patients with hepatic dysfunction were seen. In their juvenile diabetic patients Marble and his collaborators [8] noted no disturbance in hepatic function that could be determined by the usual laboratory methods, even though prominent hepatomegaly was present. Gray and his co-workers [27] in 1946 reported the serum colloidal gold reaction positive in 36.8 per cent of their diabetic patients. The percentage was higher in those receiving "irregular care." A recently published study, that of Brown,[28] recorded no disturbance in the hepatic function of 25 diabetic persons, although 15 of them were in severe acidosis.

Leevy and his co-workers [24] noted that 130 of 380 diabetic subjects had abnormal hepatic function. Thus, we see that the evidence and opinions have vacillated back and forth, seemingly without any common denominator or reason for the variance.

What about pathologic involvement? Are the livers large? Is there fatty infiltration, and does cirrhosis follow as a natural sequela?

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In 1936, it was the observation of Hanssen [29] that "medical textbooks are brief in their reference to the enlargement of the liver that is now and then found in cases of diabetes mellitus." He collected a series of 44 diabetic patients under 20 years of age, 12 of whom had enlargement of the liver; on the other hand, of 231 adult diabetic patients, in only 1 was the liver enlarged. Marble and his associates [8] cited Naunyn as stating that "in man one finds, as already described by Klebs, marked fatty infiltration of the liver." White [30] had reported on 7 young patients with hepatic enlargement, and, working with Marble, she added 60 more cases of children with diabetes, all of whom had hepatomegaly. They were of the view that evidence favors fatty infiltration as the immediate factor, based on autopsies of some of the children. Brian and associates [31] reported autopsy observations on a 24 year old diabetic man in whom the enlargement of the liver was due to glycogen deposition. Among 378 adults Warren [32] showed a slight trend toward heavier livers in diabetic patients but considered it far from striking. Moore [33] stated that the liver is usually slightly enlarged.

Anderson [34] was of the opinion that there is no characteristic change in the liver of diabetic persons but in those whose diabetes is poorly controlled it may be enlarged and yellow due to fatty infiltration. Pollack and his co-workers [35] reported hepatic fatty infiltration in 15 of 113 diabetic persons seen at autopsy (14 per cent). Robbins and Tucker [36] demonstrated significant fatty infiltration of the liver in 48 of 268 autopsies (18 per cent). It seems, then, that hepatic enlargement is much commoner in the juvenile diabetic patient, whereas in the majority of adults the enlargement, if any, is slight. Fatty infiltration in the adult does occur but is of fairly low incidence, or perhaps it is transient, and its true incidence is not discovered in autopsy material.

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29. Hanssen, P.: Enlargement of the Liver in Diabetes Mellitus, J. A. M. A. **106**:914 (March 14) 1936.

30. White, P.: Diabetes in Childhood and Adolescence, Philadelphia, Lea & Febiger, 1932, p. 169.

31. Brian, E. W.; Schechter, A. J., and Persons, E. L.: Unusual Glycogen Storage in a Case of Diabetes Mellitus, Arch. Int. Med. **59**:685 (April) 1937.

32. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938, pp. 110 and 111.

33. Moore, R. A.: Textbook of Pathology: Pathologic Anatomy in Its Relation to the Causes, Pathogenesis, and Clinical Manifestations of Disease, Philadelphia, W. B. Saunders Company, 1944, p. 1090.

34. Anderson, W. A. D.: Pathology, St. Louis, C. V. Mosby Company, 1948, p. 923.

35. Pollack, H.; Dolger, H., and Ellenberg, M.: An Analysis of the Diabetic Morbidity and Mortality in a General Hospital, Am. J. M. Sc. **202**:246 (Aug.) 1941.

36. Robbins, S., and Tucker, A. W.: The Cause of Death in Diabetes, New England J. Med. **231**:865 (Dec. 28) 1944.

Joslin [37] cited Schleusner, of Hamburg, Germany, as reporting a 12.7 per cent incidence of macroscopic hepatic cirrhosis in 355 autopsies on persons with diabetes, while Joslin was able to find only 52 cases among 10,235 (0.5 per cent) patients admitted with diabetes. Barach [38] encountered 2 cases of cirrhosis among 1,300 diabetic persons (0.15 per cent). Pollack and his co-workers [35] reported 8 among 113 diabetic patients who came to autopsy (7 per cent). Conner,[4] in his investigation of the relation of fatty infiltration to cirrhosis, reported on 2 patients with microscopically proved cirrhosis in whom diabetes had been discovered seventeen and six years before the autopsy.

The reported incidence of cirrhosis, then, varies from the high of 12.7 per cent of Schleusner to the 0.15 per cent of Barach. If the latter incidence is correct, one might question whether diabetes ever leads to cirrhosis.

EXPERIMENTAL STUDIES

Our first effort to contribute to the study consisted of determinations of liver function on 139 diabetic patients. We appreciate the limitations of the presently available tests, although Popper and his collaborators [39] noted that by using all the available tests of liver function a correct diagnosis substantiated by liver biopsy is possible in 68 to 96 per cent. We considered the retention of sulfobromophthalein (bromsulphalein®) sodium U. S. P. to be the most sensitive index, and this test was done on each patient, using 5 mg. of the dye per kilogram of body weight. The determinations used, in addition to the one with sulfobromophthalein sodium, were those of cephalin flocculation, thymol turbidity, alkaline phosphatase, serum bilirubin, urinary urobilinogen (Watson's two hour test), total protein and albumin to globulin ratio, cholesterol and cholesterol esters. At least two liver function tests were done, and, when possible, the entire profile was carried out; the average was 4.7 tests per patient.

Methods.—The following are the methods and normal values used in this laboratory:

Retention of sulfobromophthalein sodium (Rosenthal and White [40]), 0 to 5 per cent in forty-five minutes
Cephalin flocculation (Hanger [41]), 0 to 1+
Thymol turbidity (Maclagan [42]), 0 to 4 units

37. Joslin, E.; Root, H.; White, P.; Marble, A., and Bailey, C.: Treatment of Diabetes Mellitus, ed. 8, Philadelphia, Lea & Febiger, 1946, p. 544.

38. Barach, J. H.: Diabetes and Its Treatment, London, Oxford University Press, 1949.

39. Popper, H.; Steigmann, F.; Meyer, K. A.; Kozoll, D. D., and Murray, F.: Correlation of Liver Function and Liver Studies, Am. J. Med. **6**:278 (March) 1949.

40. Rosenthal, S., and White, E. C.: Clinical Application of Bromsulfalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 21) 1925.

41. Hanger, F. M.: Flocculation of Cephalin-Cholesterol Emulsion by Pathological Sera, Tr. A. Am. Physicians **53**:148, 1938; Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261 (May) 1939.

42. Maclagan, N. F.: (*a*) Thymol Turbidity Test: A New Indicator of Liver Dysfunction, Preliminary Report, Nature, London **154**:670 (Nov.) 1944; (*b*) Brit. J. Exper. Path. **25**:234 (Dec.) 1944.

Cholesterol and cholesterol esters (Bloor modification [43]), 160 to 260 mg. per hundred cubic centimeters, with a ratio of 60 per cent

Serum proteins (Weichselbaum [44]), 6.3 to 8.1 Gm. per hundred cubic centimeters

Serum bilirubin (Mallory and Evelyn [45]), 1 mg. per hundred cubic centimeters

Urobilinogen in urine (Watson [46]), 0.4 mg. in two hours

Alkaline phosphatase (Bodansky [47]), 1.5 to 4.5 units.

RESULTS

The aforementioned procedure was carried out on 139 diabetic patients; of these 46 had abnormal reactions to liver function tests. In 28 the hepatic insufficiency could be explained on other bases than diabetes: chronic alcoholism, 15; heart disease with history of failure, 6; heart disease with auricular fibrillation, 1; chronic hepatitis, 2; malnutrition, 1; cholecystitis with cholelithiasis, 2; far advanced tuberculosis, 1. In the remaining 18 patients no disease other than diabetes was present which could explain the impaired liver function.

In all except 4 the sulfobromophthalein retention alone was abnormal. Concerning diabetic control, the following arbitrary classification was based on the blood sugar level at the patient's admission, to the hospital, as well as his past records: good, blood sugar level less than 200 mg.; fair, blood sugar between 200 and 300 mg.; poor, blood sugar level over 300 mg., per hundred cubic centimeters. The condition of any patient who had a history of diabetic coma, severe acidosis or a severe insulin reaction was classified as poor, regardless of the blood sugar level during his current admission. Any new diabetic patient was listed as uncontrolled. With the use of these criteria, 12 of the patients were in either the poor or the uncontrolled group (table 2). It is of interest that in the complete series there were 7 patients admitted in moderate to severe acidosis (precoma to coma) and 1 with a severe insulin reaction. Of the 7 in acidosis 3 had an abnormal result on liver function tests; 1 patient had a thymol turbidity of 12 units, which returned to normal in seven days, and 1 patient had a sulfobromophthalein retention of 7 per cent, which returned to normal in thirty days. The remaining patient had a

43. Bloor, W. R.: Cholesterol in Blood, J. Biol. Chem. **24**:227 (March) 1916.

44. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path. (Tech. Sect.) **10**:40 (March) 1946.

45. Mallory, H. T., and Evelyn, K. A.: Determination of Bilirubin with Photo-Electric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

46. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: Studies of Urobilinogen: Simple Method for Quantitative Recording of Ehrlich Reaction as Carried out with Urine and Feces, Am. J. Clin. Path. **14**:605 (Dec.) 1944.

47. Bodansky, A.: Phosphatase Studies: Determination of Serum Phosphatase; Factors Influencing Accuracy of Determination, J. Biol. Chem. **101**:93 (June) 1943.

TABLE 1.—*Data on Diabetic Patients with Abnormal Results on Liver Function Tests*

Patient	BSP* Retention, %	Thymol Turbidity, Units	Cephalin Flocculation	Alkaline Phosphatase, Units	Bilirubin, Mg./100 Cc.	Albumin/Globulin, Gm./100 Cc.	Urinary Urobilinogen, Mg./2 Hr.	Cholesterol/Cholesterol Esters, Mg./100 Cc.	Age, Yr.	Complications
G. S.	6	3	.....	4.5	0.5	.....	.....	.....	55	None
H. C.	12	2	.....	3.2	0.5	4.2/2.8	.....	.....	31	None
W. E.	5	4	.....	3.3	0.5	.....	.....	208/162	33	None
J. W.	9	6	.....	...	...	5.1/3.2	.....	.....	58	None
M. G.	9	2	.....	2.8	0.5	4.9/2.8	.....	210/162	53	Obesity
D. B.	12	3	.....	5.0	0.5	4.1/1.9	0.415	188/88	22	None
B. D.	0	20	Neg.	...	0.5	4.1/3.4	0.415	.....	53	None
E. G.	7	2	.....	...	0.5	4.8/2.9	.....	139/103	50	Acidosis
J. R.	0	12	Neg.	2.7	...	.....	.....	189/108	29	Acidosis
H. H.	6	2	.....	3.2	1.0	.....	.....	363/200	50	None
J. S.	6	1	.....	6.9	...	4.2/2.9	.....	.....	37	Hypoglycemia
H. D.	20	2	Neg.	3.9	0.5	3.1/3.1	0.15	170/100	58	None
D. G.	9.4	2	.....	...	0.5	4.4/2.3	.....	.....	56	None
P. M.	11	12	2+	...	0.5	4.0/2.6	0.16	196/155	51	None
H. P.	11	3	.....	3.0	0.5	3.6/2.7	0.28	213/159	37	None
S. B.	11	6	.....	...	...	5.2/3.1	0.15	.....	52	Hypertension
H. W.	8	3	.....	5.4	0.5	4.0/2.7	.....	250/151	58	Obesity
D. M.	0	2	.....	...	5.6	4.4/2.8	.....	.....	22	Acidosis
R. T.	20	..	Neg.	5.0	...	.....	.....	.....	72	Auricular fibrillation
H. A.	25	4	Neg.	...	...	.....	.....	.....	44	Alcoholism
J. F.	20	11	2+	7.0	0.5	3.2/3.8	0.1	.....	55	Alcoholism
E. G.	0	8	.....	8.9	1.5	3.4/3.1	.....	.....	53	Cardiac disease
A. H.	5	..	Neg.	...	...	3.4/2.6	.....	152/122	65	Cardiac disease
Q. H.	13	9	2+	2.4	...	3.6/3.6	.....	.....	35	Chropic hepatitis
J. K.	10	1	.....	2.9	0.5	4.2/3.0	0.15	290/194	65	Alcoholism
P. K.	38	6	Neg.	6.0	5.0	3.2/2.1	.....	161/80	59	Cardiac disease
J. L.	5	4	.....	2.9	3.5	.....	.....	.....	54	Alcoholism
M. B.	16	1	.....	...	0.7	4.8/2.7	.....	.....	59	Cholecystitis
J. M.	7	5	.....	...	1.8	4.5/2.4	.....	.....	53	Alcoholism
N. M.	12	2	.....	3.2	0.5	4.6/2.6	0.24	210/140	54	Cholecystitis
J. R.	10	..	Neg.	...	...	4.3/3.0	.....	.....	57	Alcoholism
E. G.	24	1	.....	...	3.0	.....	.....	.....	59	Alcoholism
W. G.	9.4	1	.....	...	0.5	3.2/1.8	.....	.....	47	Alcoholism
A. M. G.	11	2	.....	3.3	0.5	3.8/2.6	0.6	166/124	51	Hepatitis
A. G.	10	9	.....	4.6	...	2.9/2.7	0.15	315/180	52	Alcoholism
F. H.	5	2	.....	2.8	0.7	.....	.....	.....	39	Malnutrition
J. H.	13	2	.....	3.4	0.5	4.3/2.1	.....	.....	54	Cardiac disease
H. H.	5	..	Neg.	...	0.5	4.3/2.2	.....	.....	49	Alcoholism
J. K.	13	10	.....	2.8	0.5	4.4/2.4	.....	.....	57	Alcoholism
B. M.	10	6	.....	...	0.8	3.8/2.7	.....	.....	53	Alcoholism
J. Mc.	15	2	.....	11.4	0.5	4.0/2.4	.....	.....	57	Alcoholism
A. P.	24	2	.....	2.8	0.5	3.3/2.7	.....	.....	61	Alcoholism
A. R.	7	2	1+	...	...	.....	.....	.....	53	Cardiac disease
W. A.	15	1	.....	19.5	0.5	3.8/3.6	.....	.....	53	Tuberculosis
A. W.	43	2	.....	...	...	3.4/1.9	.....	.....	60	Cardiac disease
R. W.	49	20	.....	...	0.5	2.5/2.9	.....	.....	41	Alcoholism

* In this and the following tables BSP indicates sulfobromophthalein ("bromsulphalein") sodium.

TABLE 2.—*Control of Diabetes*

	Good	Fair	Poor	Uncontrolled (New Diabetic Patients)	Total No. of Patients
Total study group	30	30	32	38	130
Abnormal results on hepatic function tests with and without explanation	11	11	13	11	46
Abnormal results on hepatic function tests without explanation	3	3	6	6	18

transient rise in serum bilirubin. The patient with the insulin reaction had an abnormality of sulfobromophthalein retention which persisted on recheck six months later. From the table regarding control of diabetes (table 2) it may be seen that 24 of 70 patients whose condition was poor and uncontrolled (34.3 per cent) and 22 of 69 whose condition was fair and well controlled (31.8 per cent) had abnormal results on liver func-

TABLE 3.—*Duration of Diabetes*

	Less Than 1 Yr.	1 to 5 Yr.	5 to 10 Yr.	10 to 20 Yr.	20 Yr. and Over	Total No. of Patients
Total study group	43	43	32	11	10	139
Abnormal results on hepatic function tests with and without explanation	11	16	9	5	4	46
Abnormal results on hepatic function tests without explanation	5	5	4	3	1	18

TABLE 4.—*Follow-up Examinations on Diabetic Patients with Original Abnormal Results on Liver Function Tests*

Patient	Yr. of Diabetes	Control	Abnormal Results on Tests	Results on Reexamination	Time Interval	Palpable Liver, Cm.	Palpable Liver on Reexamination
G. S.	1	Fair	BSP, 6%	BSP, 0	1 yr.	4	No
H. W.	5	Poor	BSP, 8%	BSP, 0	3 mo.	No	No
P. M.	New	Uncontrolled	BSP, 11%; thymol, 12 units	BSP, 0; thymol, 7 units	17 mo.	2	No
H. P.	4	Fair	BSP, 11%	BSP, 0	18 mo.	4	No
H. H.	26	Poor	BSP, 6%	BSP, 0	7 mo	No	No
J. S.	9	Poor	BSP, 6%	BSP, 7%	6 mo.	No	No
D. G.	1	Good	BSP, 9%	BSP, 0	15 mo.	No	No
S. B.	New	Uncontrolled	BSP, 11%	BSP, 0	2 mo.	6	6 cm.
H. C.	New	Uncontrolled	BSP, 12%	BSP, 0	8 mo.	No	No
H. D.	5	Poor	BSP, 20%	.....	.....	No	No
J. R.	New	Uncontrolled	Thymol, 12 units	Thymol, 2 units	7 days	No	No
E. G.	11	Poor	BSP, 7%	BSP, 0	1 mo.	No	No
B. D.	12	Poor	Thymol, 20 units	.....	.....	2	...
D. B.	New	Uncontrolled	BSP, 12%	BSP 0	17 days	No	No
M. G.	14	Fair	BSP, 9%	.....	.....	No	...
W. E.	1	Good	BSP, 5%	.....	.....	No	...
J. W.	8	Good	BSP, 9%; thymol, 6 units	.....	.....	8	...
D. M.	3	Poor	Serum bilirubin, 5.6 mg.	.....	.....	No	...

tion tests. In the group with unexplained abnormal results 12 of the 70 with a poor and uncontrolled condition (17.1 per cent) and 6 of the 69 with a fair and well controlled condition (8.6 per cent) had evidence of hepatic dysfunction.

The duration of the diabetes is shown in table 3; of our 18 patients under consideration, 10 had diabetes less than five years. In order to determine the persistence of the hepatic abnormalities, we were able to recheck 12 of the 18 patients (the remainder were not available). In all but 2 of these 12 patients the results of liver function tests had returned

to normal. In the 36 patients with palpable livers 4 were reexamined and in only 1 was the organ still palpable; in patient S. B. there was no change in the hepatic size.

The second phase of our investigation was an attempt to contribute information toward the questions: 1. What evidence is there of cirrhosis in diabetes? 2. Can cirrhosis lead to a true diabetic state? We searched the records of this hospital from 1940 through 1949 for all patients with a combined diagnosis of cirrhosis and diabetes. Thirty-six cases among 3,543 patients admitted for diabetes were found in which we could agree with this diagnosis. For the diagnosis of diabetes in this series we

TABLE 5.—*Diabetes Developing in Cirrhotic Patients*

Patient	Age at Diagnosis of Cirrhosis	Diagnosis of Diabetes Made in Same Yr.	Control	Alcoholism	Autopsy Diagnosis
P. O.	50	+	Diet	+	+
E. P.	52	+	28 units protamine zinc insulin	+	..
L. W.	48	+	Diet	+	..
C. M.	44	+	40 units protamine zinc insulin	..	..
			20 units regular insulin	+	+
N. H.	51	+	Diet	+	+
J. M.	57	+	Diet	..	..
C. Z.	42	+	Regular insulin	+	+
R. W.	41	+	10 units 2:1 insulin mixture	+	..
J. M.	48	+	12 units protamine zinc insulin	+	Biopsy
J. O.	47	+	40 units protamine zinc insulin	..	..
J. F.	48	+	48 units 2:1 insulin mixture	+	..
E. Q.	57	+	30 units protamine zinc insulin	+	..
H. A.	57	+	Diet	+	..
E. S.	48	+	12, 10, 10 units insulin	+	+
H. B.	49	+	30 units protamine zinc insulin	+	..
E. S.	57	+	Diet	+	..
O. O.	61	+	Diet	..	..
O. S.	67	+	12, 12, 12 units insulin	+	..
J. C.	54	+	Regular insulin	..	+
J. M.	51	+	Diet	+	..
S. B.	46	+	24 units protamine zinc insulin	+	+

required either a fasting blood sugar level above 200 mg. per hundred cubic centimeters or a dextrose tolerance curve in which the blood sugar failed to return to 160 mg. per hundred cubic centimeters or the preinjection level, whichever was higher, in two hours. We used these high criteria to attempt to satisfy any objections as to whether we were dealing with the diabetic syndrome or only hepatic hyperglycemia. At this point we should like to state that we realize there may be criticism regarding even these criteria, and we will not say that it is unwarranted. That a few of our lower curves may represent only hepatic hyperglycemia is a possibility. One might anticipate a revision of the criteria in the future as the definition and understanding of diabetes mellitus are made more clear. The diagnosis of cirrhosis was based either on autopsy observations

(11 patients) or on the presence of persistent hepatomegaly with notably abnormal results on liver function tests. All doubtful cases were discarded. Thirty-one of the 36 patients were chronically alcoholic. In 15 patients the diabetes preceded the cirrhosis, while in 21 the reverse was true. In these 15 patients all except 1 had been a heavy consumer of alcohol for many years. There were 6 who received the diagnosis of diabetes five years or more before that of cirrhosis.

Patient W. G. was found to be diabetic in 1926. The patient denied any history of jaundice, alcoholism or acute hepatitis. His diabetes was adequately controlled on diet alone until 1935, when administration of regular insulin in daily dosage of 10, 5 and 5 units was begun. He was not seen again until 1947, at which time he entered the hospital with tarry stools, abdominal ascites, peripheral edema and a blood sugar level of 400 mg. per hundred cubic centimeters. His course was progressively downhill, and he died. Autopsy revealed portal cirrhosis with esophageal varices. This patient was the only one in which no cause other than diabetes could be found for the cirrhosis, and, even then, prior to his last admission the diabetes was mild.

TABLE 6.—*Cirrhosis Developing in Diabetic Patients*

Patient	Age at Diabetic Diagnosis	No. Yr. Before Diagnosis of Cirrhosis	Control	Alcoholism	Autopsy Diagnosis
J. L.	56	1	18 units protamine zinc insulin	+	..
J. C.	51	1	Diet	+	+
J. R.	55	2	Diet	+	..
B. R.	36	2	Diet	+	..
B. M.	52	2	Diet	+	..
J. S.	64	2	Diet	+	+
H. E.	51	3	12 units protamine zinc insulin	+	..
P. K.	54	4	Diet	+	..
H. W.	62	3	28 units protamine zinc insulin	+	..
J. K.	58	6	20 units protamine zinc insulin	+	..
B. V.	40	6	15 units protamine zinc insulin	+	..
J. P.	49	7	Diet	+	..
W. F.	54	8	Diet	+	..
W. G.	40	21	10, 5, 5 units insulin	..	+
A. V.	27	24	Diet	+	+

Of our group of 21 diabetic cirrhotic patients 14 required insulin to control the hyperglycemia; of the group of 15 cirrhotic diabetic patients 6 required insulin. No specific data on diabetic control with variations in hepatic damage can be given, but, in general, after the diagnosis of diabetes was made, the diet and insulin requirements changed in these patients no more than one would expect them to change in any other diabetic persons.

COMMENT

From a review of the literature it is apparent that severe hepatic damage can lead to hypoglycemia through a reduction in and even loss of the liver's ability to maintain the blood sugar level. This is confirmed

by the experimental removal of the liver in dogs, producing severe hypoglycemia. We do not mean to imply that all patients with severe hepatic damage have this symptom, but it does occur and certainly its possibility should be kept in mind in the management of disease of the liver.

Decreased dextrose tolerance has been noted in acute infectious diseases, obesity, hepatitis and biliary tract disease. In each case hepatic dysfunction has been suggested. Experimentally, diphtheria toxin has been used to decrease dextrose tolerance in pancreatectomized dogs. Hepatectomized dogs maintained on dextrose feedings gave diabetic type curves.

In 21 of our 36 diabetic cirrhotic patients the diagnosis of cirrhosis preceded that of diabetes. In the remaining group in only 6 was there as much as five years separating these diagnoses, and in none of these was cirrhosis ruled out at the time of the diabetic diagnosis. It is not possible to say with any conviction that the cirrhosis was the direct cause of the diabetic state. One could argue that the cirrhosis merely brought on latent diabetes or that the onset of the diabetes was coincident but not related. Was it really a diabetic state? The criticism of the diabetic criteria has been referred to elsewhere in this paper. There was a tendency toward a flatter type curve in our cirrhotic diabetic patients however. Fourteen of the 21 diabetic cirrhotic patients and 6 of the 15 cirrhotic diabetic persons had diabetes of sufficient severity to require insulin. One recent patient, not mentioned in this series, had normal dextrose tolerance. Six months later, after the continuous partaking of alcoholic beverages, his dextrose tolerance curve was diabetic on two tests, and his urine continued to contain sugar. It remains only for time to determine whether or not he is now diabetic.

It is quite tempting to make the statement that in an occasional instance cirrhosis can bring about a permanent diabetic syndrome, but we shall resist that temptation, offer only our material and suggestions and refrain from drawing any unwarranted conclusions.

It is our opinion that there is a tendency to refer loosely to the large fatty liver of the diabetic person as a frequent occurrence. The literature does not bear out such frequency except in juveniles. There now can be no question concerning the frequent occurrence of hepatic enlargement in young diabetic subjects, which may well be due to fatty infiltration. In adults, however, although hepatomegaly and fatty infiltration do occur, the incidence is fairly low, and in the extensive series of Warren the indication was only toward a trend to heavier livers.

If we follow the theory that hepatic cirrhosis is preceded by fatty infiltration, since the incidence of appreciable infiltration in the adult

diabetic patient is not high, then we would not expect to find a high incidence of cirrhosis. The few reports available indicate that this is true. In our series of 36 diabetic patients in whom cirrhosis was found, only one did not have some more acceptable etiologic reason for the cirrhosis than diabetes. He was 1 in 3,543 admissions, giving an incidence of 0.028 per cent. If we considered that the causation in the entire group of 15 patients is diabetes (which certainly is not true), then the incidence is still lower than the incidence of cirrhosis in the general population. Ratnoff and Patek,[48] in a survey, found the incidence of cirrhosis in the United States based on autopsy material to be between 0.43 and 6.3 per cent. We, therefore, believe that the role of diabetes in cirrhosis is questionable.

In our study of hepatic function, 46 of 139 diabetic patients gave abnormal results. In 28 of these patients it was possible to explain this finding by factors other than diabetes, i. e., chronic alcoholism, cardiac disease with episodes of failure, etc., but in 18 no other cause could be found, an incidence of 12.9 per cent. In this group there was a ratio of 2 to 1 in favor of hepatic insufficiency in the patients whose diabetes was not well controlled. We were able to recheck 12 of these 18 patients at a later date, and in all but 2 the hepatic function had returned to normal. It is our belief that hepatic dysfunction, as determined by the available tests, in diabetes is not common; when it does occur, it is transient in nature and extremely rarely, if ever, leads to permanent damage. There is a tendency for the dysfunction to vary directly with diabetic control. Among these patients 6 were observed to have enlarged livers; 4 were reexamined, and in only 1 did the liver remain enlarged.

In the remaining 28 patients we cannot exclude diabetes as a factor in the hepatic dysfunction. Certainly 45 of 139 patients is a high incidence of hepatic damage in any study group, but then this study was not done on consecutive patients but on selected ones, patients that we thought would show hepatic disease. The combination of alcoholism, heart failure, etc., with diabetes may make the liver more susceptible to temporary damage than any one of the diseases alone, but, in view of the lack of knowledge of the cause of hepatic abnormalities, we know of no way to prove or disprove this observation. One should search for more acceptable etiologic agents in the majority of hepatic abnormalities in diabetic patients.

It may be that mild hepatic damage by various agents could be brought to light by hepatic function tests more readily in the presence of uncontrolled diabetes than when carbohydrate metabolism is normal.

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48. Ratnoff, O. P., and Patek, A. J., Jr.: Natural History of Laennec's Cirrhosis of Liver: Analysis of 386 Cases, Medicine **21**:207 (Sept.) 1942.

SUMMARY

One hundred and thirty-nine diabetic patients were studied with liver function tests. Forty-six had abnormal results, but in only 18 (12.9 per cent) were we unable to find another cause. There was a tendency for dysfunction to vary directly with diabetic control. Thirty-six patients with diabetes and cirrhosis were collected from 3,543 admitted with diabetes. In only 1 was diabetes the only possible etiologic agent found, an incidence of 0.028 per cent. The incidence of hepatomegaly and fatty infiltration in adults with diabetes is fairly low. Hepatic dysfunction in diabetes is of low incidence but is transient in nature and seldom, if ever, leads to permanent damage.

INFECTIOUS MONONUCLEOSIS WITH HEPATITIS

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PHYSICIANS in the past have designated infectious mononucleosis as an acute benign infectious disease of unknown causation with protean manifestations. Classically, it was recognized as primarily affecting the nasopharynx, accompanied with lymph node enlargement, splenomegaly, the appearance of large atypical bizarre lymphocytes in the peripheral blood and the development of heterophil agglutinations for sheep red cells as exemplified in the Paul-Bunnell test. The course is usually mild, the prognosis excellent and treatment symptomatic. However, reports of the occurrence of cutaneous eruptions, purpura and other hemorrhagic manifestations, pneumonitis, myocardial involvement, nephritis, meningeal irritation and a "visceral" or typhoidal type of infection without any peripheral local manifestations have testified to the fact that infectious mononucleosis is really a generalized infection.[1]

In view of these various manifestations of the disease Tidy [2] distinguished three main types, dependent on the pertinent clinical features: 1. The glandular form occurs predominantly in children and is manifested after a short prodromal period by the development of enlargement of all or any group of lymph nodes. The cervical nodes are the most frequently involved, and next in order of frequency is involvement of the axillary and inguinal nodes. Constitutional symptoms may or may not be present in this form of the disease. 2. The anginose type has often been clinically confused with tonsillitis, pharyngitis or diphtheria. The throat may be diffusely injected or the appearance may suggest

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1. Hepatitis in Infectious Mononucleosis, Editorial, Ann. Int. Med. **28**:1059, 1948.

2. Tidy, H. L.: Glandular Fever and Infectious Mononucleosis, Lancet **2**:180 and 236, 1934.

follicular tonsillitis or membranous pharyngitis. In fact, in severe cases a membrane may persist for days and edema may develop, although laryngeal obstruction has not been reported. Vincent's infection is a common complication. 3. The febrile type is common in adults, the onset being sudden, with malaise, fever, headache and frequently chills. The headache may be severe enough to suggest the presence of meningitis. Lymph node enlargement may appear in that type of disease at any point in the course of the illness.

In earlier days it was possible to distinguish between an epidemic form, in which 80 per cent of the cases were observed in children, and a sporadic form occurring in older children and young adults. However, since World War II, cases have been reported involving persons of all age groups. There seems to be a slightly increased tendency for the disease to appear in males as compared with females, and up until World War II it had been reported that not a single case of this disease had occurred in Negroes. However, Wechsler and his associates,[3] in a large series of 556 cases reported from an Army camp, revealed that the incidence of this disease in Negro Army personnel was higher than the over-all comparable proportion of Negro personnel at the post. It is felt that the absence of descriptions of this disease in Negroes prior to the report of this large series was due to the fact that, for the most part, Negroes are less frequently hospitalized and less frequently have laboratory work done which would have made the diagnosis possible. No etiologic agent for infectious mononucleosis has been definitely shown, but the current concept is that the disease is probably due to a virus.

DIAGNOSIS

Characteristic physical findings include the presence of fever, which may vary from a mild degree of elevation of temperature to as high as 104 F. The spleen is palpably enlarged in at least 50 to 60 per cent of patients.[4] Spontaneous rupture of the spleen has been reported in several patients.[5] As a rule, enlargement is not great. The liver has been reported palpable in 12 to 20 per cent of patients [4b] and is usually tender to palpation.

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3. Wechsler, H. F.; Rosenblum, A. H., and Sills, C. T.: Infectious Mononucleosis: Report of an Epidemic in an Army Camp, Ann. Int. Med. **25**:113 and 236, 1946.

4. (*a*) Tidy.[2] (*b*) Bernstein, A.: Infectious Mononucleosis, Medicine **19**:85, 1940.

5. (*a*) Ziegler, E. E.: Infectious Mononucleosis: Report of a Fatal Case with Autopsy, Arch. Path. **37**:196 (March) 1944. (*b*) Fisher, J. H.: Visceral Lesions of Acute Infectious Mononucleosis: A Report of 2 Cases with Fatal Spontaneous Rupture of Spleen, Am. J. Path. **42**:651, 1946. (*c*) Ricker, W.; Blumberg, A.; Peters, C. H., and Widerman, A.: The Association of the Guillain-Barré Syndrome with Infectious Mononucleosis, with Report of 2 Fatal Cases, Blood **2**:217, 1947.

Cardiac and pulmonary signs are uncommon, although several cases of abnormal electrocardiograms have been reported,[6] indicating either diffuse myocardial or probable pericardial involvement. The incidence of hematuria has been reported as 6 per cent in some series.[2] Hemorrhagic manifestations are infrequent and include epistaxis, hematuria, rectal bleeding and purpura. These are often associated with thrombocytopenia, which apparently is a manifestation of hypersplenism. Skin manifestations include a macular or maculopapular rash resembling a typhoidal or at times scarlatiniform rash, usually involving the trunk and upper arms.

The classic diagnostic features consist of the increased concentration of abnormal lymphocytes in the peripheral blood smear and a positive Paul-Bunnell reaction. The characteristic feature of the blood smear is an increase in lymphoid cells, which are of three types. There is an increase in small lymphocytes and in monocytes. Both appear normally in the peripheral blood. More important, large monocytoid lymphocytes appear, which are not normally observed in the peripheral blood. These abnormal cells vary in size and shape, containing an irregularly shaped nucleus and a cytoplasm which is usually vacuolated or foamy in appearance. The cytoplasm may contain granules, and rarely the nucleus appears blastic. The total leukocyte count may vary. The characteristic feature, however, is usually a normal or slightly elevated total white blood cell count at the onset of the disease, with the development of leukopenia and relative lymphocytosis as the disease progresses.

The other important test diagnostic of infectious mononucleosis is the so-called Paul-Bunnell test, also known as the heterophil antibody reaction.[7] The principle of this test is that the serum of patients with infectious mononucleosis contains agglutinins against sheep red cells in high titer. This test has been variously reported as giving positive reactions in 60 to 92 per cent of cases.[4b] The test is highly specific for this disease, although false positive reactions have been shown in persons receiving horse serum for some dissociated condition. Liver extract given parenterally may also produce increased titer. There are several adsorption tests using extracted guinea pig kidney or ox cells which will aid in differentiating those agglutinins not due to infectious mononucleosis.[8]

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6. Evans, W. F., and Graybiel, A.: Electrocardiographic Evidence of Cardiac Complication in Infectious Mononucleosis, Am. J. M. Sc. **211**:220, 1946.

7. Paul, J. R., and Bunnell, W. W.: The Presence of Heterophile Antibodies in Infectious Mononucleosis, Am. J. M. Sc. **183**:90, 1932.

8. Davidsohn, I., and Walker, P.: The Nature of the Heterophile Antibodies in Infectious Mononucleosis, Am. J. Clin. Path. **5**:455, 1935.

HEPATITIS IN INFECTIOUS MONONUCLEOSIS

Recently, several investigators have reported on the incidence of hepatitis as a manifestation and/or complication of infectious mononucleosis. This appears to be a matter of considerable significance in our management of infectious mononucleosis. Jaundice was first recognized as a complication of infectious mononucleosis by Mackey and Wakefield [9] in 1926, although a single case had been noted previously by Downey and McKinlay.[10] The incidence of jaundice in previously reported series has varied from 1.3 to 12.8 per cent.[11] It was first felt that the jaundice was due to obstruction of the common bile duct by extrinsic pressure from enlarged abdominal lymph nodes, although, undoubtedly because of the rarity of fatalities in this disease, no direct proof of such mechanism has ever been produced. Later studies in which punch biopsies of the liver were performed in patients having infectious mononucleosis with jaundice showed focal regions of hepatitis in the portal areas, with cloudy swelling of the hepatic cells, focal necrosis and infiltration with mononuclear cells, resembling the lesions seen in infectious hepatitis.[12]

Wechsler and his co-workers,[8] in their large series of 556 patients, reported on 34 patients (6 per cent) with jaundice. They stated that the clinical picture was indistinguishable from infectious hepatitis except that the icterus cleared more rapidly and gastrointestinal symptoms were milder. Quantitative van den Bergh determinations were abnormal in all patients tested. Cephalin flocculation in 23 of 25 patients was abnormal. In 9 of 27 patients, the cholesterol level was high and paralleled the icterus index. In 13 patients tested, there were varying amounts of abnormal retention of sulfobromophthalein (bromsulphalein®) sodium. The dextrose tolerance curve was abnormal in 9 of 11 patients. The Watson test gave a normal result in 12 cases. The liver was enlarged in 17 per cent of all these patients with infectious mononucleosis and was accompanied with tenderness in those with jaundice.

Until recently, however, little or no emphasis has been placed on studies of hepatic function in nonjaundiced persons with infectious mononucleosis. Ziegler [5a] reported the autopsy observations on a patient

9. Mackey, R. P., and Wakefield, E. G.: The Occurrence of Abnormal Leukocytes in the Blood of a Patient with Jaundice (Infectious Monomucleosis), Ann. Clin. Med. **4**:727, 1926.

10. Downey, H., and McKinlay, C. A.: Acute Lymphadenosis Compared with Acute Lymphatic Leukemia, Arch. Int. Med. **32**:82 (July) 1923.

11. Immerman, S. L.: An Epidemic of Infectious Mononucleosis, M. Rec. **157**:480, 1944. Spring, M.: Jaundice in Infectious Mononucleosis, Bull. U. S. Army M. Dept., 1944, no. 81, p. 102.

12. Kilham, L., and Steigman, A. J.: Infectious Monomucleosis, Lancet **2**:452, 1942. Bang, J., and Wanschen, O.: Histopathology of the Liver in Infectious Mononucleosis Complicated by Jaundice, Acta med. Scandinav. **120**:437, 1945.

with infectious mononucleosis who died of spontaneous rupture of the spleen. He observed microscopic changes in the liver similar to those seen in the jaundiced patients previously mentioned.[5b, c]

Cohen and Lidman [13] reported on 16 consecutive patients without jaundice, in all of whom abnormal hepatic function was demonstrated by the reactions to two or more tests. The thymol turbidity reaction was most consistently positive; abnormal sulfobromophthalein retention and increased alkaline phosphatase were noted in some patients.

Carter and Maclagan [14] reported the thymol turbidity reaction abnormal in 58 per cent of 18 patients. DeMarsh and Alt [15] studied 19 patients. They observed the cephalin flocculation to be positive in 15 of 18 patients and abnormality of sulfobromophthalein retention in 15 of 19. In most of their series hepatic function returned to normal in two to six weeks, but in 3 patients it remained abnormal for two to four and one-half months. Cohen and Lidman [13] also mentioned one patient in whom chronic hepatitis developed.

Evans [16] studied 19 patients and reported cephalin cholesterol flocculation positive in 95 per cent, thymol turbidity positive in 68 per cent and the alkaline phosphatase level elevated in 43 per cent. It was concluded that in the presence of jaundice it is difficult to distinguish infectious mononucleosis from infectious hepatitis. The hematologic picture of both is similar (Barker and associates [17] reported that the atypical lymphocytes may be as high as 60 per cent). The reaction to the Paul-Bunnell test, however, has not been reported as positive in infectious hepatitis, and it is felt that this test furnishes the most reliable means at present to distinguish the two conditions.

PRESENT STUDY

We have become interested in the problem of hepatic involvement in this disease, not so much because of its investigative significance but because of its clinical importance in our management and treatment of patients. Heretofore, it has been the custom to consider infectious mononucleosis as a self-limiting disease requiring little or no treatment other than symptomatic medication. However, if an associated hepatitis

13. Cohen, C., and Lidman, B. L.: Hepatitis Without Jaundice in Infectious Mononucleosis, J. Clin. Investigation **25**:145, 1946.

14. Carter, A. B., and Maclagan, N. F.: Some Observations on Liver Function Tests in Diseases Not Primarily Hepatic, Brit. M. J. **2**:80, 1946.

15. DeMarsh, Q. B., and Alt, H. L.: Hepatitis Without Jaundice in Infectious Mononucleosis, Arch. Int. Med. **80**:257 (Aug.) 1947.

16. Evans, A. S.: Liver Involvement in Infectious Mononucleosis, J. Clin. Investigation **27**:106, 1948.

17. Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theater, Including Acute Hepatitis, Without Jaundice, J. A. M. A. **128**:997 (Aug. 4) 1945.

is present, it appears proper that more vigorous attention and care be given to the management of these patients to insure a proper restorative response on the part of the liver and to avoid possible development of chronic hepatitis and ultimate cirrhosis. We now have available the data on 90 patients with infectious mononucleosis treated at this hospital in the last thirty-six months. On all these patients, tests for heterophil antibody reaction and examinations of the peripheral blood smears for the presence of abnormal lymphocytes were performed; the diagnosis was considered as established if any two of the following three criteria were present: (1) characteristic clinical signs and symptoms; (2) positive heterophil antibody reaction in a titer of 1:56 or higher; (3) presence of atypical lymphocytes in the peripheral blood smear.

A variety of liver function tests was performed on all these patients, but unfortunately it was not possible to perform all the tests on all the patients, owing to limitation of capacity of the clinical laboratory. The tests performed and methods and normal values used in this laboratory are as follows:

Thymol turbidity test (Maclagan [18]), 0 to 4 units.

Quantitative van den Bergh test (Mallory and Evelyn [19]), direct reaction, 0.15 mg.; indirect reaction, 0.5 mg., per hundred cubic centimeters.

Sulfobromophthalein retention (Rosenthal and White [20]), 0 to 5 per cent in forty-five minutes.

Serum proteins (Weichselbaum [21]), 6.3 to 8.1 Gm. per hundred cubic centimeters.

Alkaline phosphatase (Bodansky [22]), 1.5 to 4.5 units.

Cephalin flocculation (Hanger [23]), 0 to 1+.

Urinary urobilinogen (Watson [24]), 0.4 mg in two hours.

Cholesterol and cholesterol esters (Bloor [25] modification), 160 to 260 mg. per hundred cubic centimeters; ratio of cholesterol to cholesterol esters, 60 per cent.

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18. Maclagan, N. F.: Thymol Turbidity Test: A New Indicator of Liver Dysfunction, Nature, London **154**:670, 1944; The Thymol Turbidity Test as an Indicator of Liver Dysfunction, Brit. J. Exper. Path. **25**:234, 1944.

19. Mallory, H. T., and Evelyn, K. A.: Determination of Bilirubin with Photo-Electric Colorimeter, J. Biol. Chem. **119**:481, 1937.

20. Rosenthal, S., and White, E. C.: Clinical Application of Bromsulfalein Test for Hepatic Function, J. A. M. A. **84**:1112 (April 21) 1925.

21. Weichselbaum, T. E.: An Accurate and Rapid Method for the Determination of Proteins in Small Amounts of Blood Serum and Plasma, Am. J. Clin. Path. (Tech. Sect.) **10**:40, 1946.

22. Bodansky, A.: Phosphatase Studies: Determination of Serum Phosphatase; Factors Influencing Accuracy of Determination, J. Biol. Chem. **101**:93, 1943.

23. Hanger, F. M.: Flocculation of Cephalin-Cholesterol: Emulsion of Pathological Serum, Tr. Am. A. Physicians **53**:148, 1938; Serological Differentiation of Obstruction from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, J. Clin. Investigation **18**:261, 1939.

24. Watson, C. J.; Schwartz, S.; Sborov, V., and Bertie, E.: Studies of Urobilinogen: Simple Method for Quantitative Recording of Ehrlich Reaction as Carried Out with Urine and Feces, Am. J. Clin. Path. **14**:605, 1944.

25. Bloor, W. R.: Cholesterol in Blood, J. Biol. Chem. **24**:227, 1916.

Often it was necessary to repeat the heterophil antibody test on several occasions before a significant titer was obtained. In many patients a rapid rise and a rapid fall in titer were noted, so that it would appear necessary to perform serial tests at frequent intervals, twice weekly, in order not to miss a significantly elevated titer.

RESULTS

In figure 1 are the presenting complaints of 50 consecutive patients. Fever was the commonest symptom, occurring in 90 per cent of these patients. Headache and chilliness each were complaints in 60 per cent,

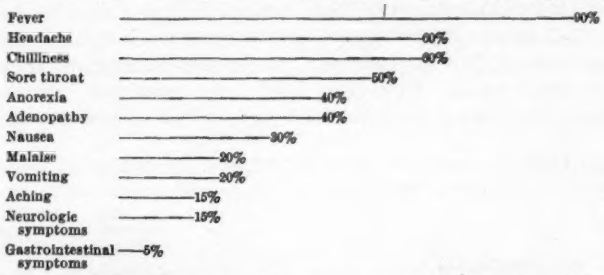

Fig. 1.—Graph showing presenting complaints of infectious mononucleosis among 50 consecutive patients.

and sore throat occurred in 50 per cent. In 40 per cent of the group loss of appetite and in another 40 per cent swollen lymph nodes were presenting complaints. It is interesting to note the diagnoses on admission made from these symptoms varied from a correct diagnosis in 47 per cent of the patients to such clinical impressions as fever of undetermined origin, pharyngitis, poliomyelitis, influenza, blood dyscrasia, diphtheria and nephritis.

The abnormal physical findings in these patients, as seen in figure 2,

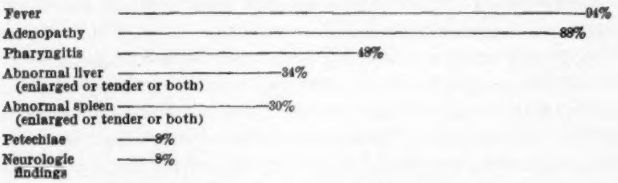

Fig. 2.—Graph showing incidence of physical findings.

in order of decreasing frequency were fever (94 per cent), adenopathy (88 per cent), pharyngitis (48 per cent), enlarged or tender liver (34 per cent) and palpable or tender spleen (30 per cent). Petechiae of the

mucous membranes were an additional sign, while abnormal neurologic findings were less common.

The heterophil antibody reactions obtained in 90 patients were analyzed. Of these 90 patients, 81, or 90 per cent, revealed the presence of heterophil antibodies in significant titer at some time during the course of the disease. Nine per cent showed a titer of 1:28 or 1:56 and 20 per cent a titer of 1:112. Seventy-one per cent had a titer of 1:224 or higher. In reviewing these results, we should like to reemphasize the fact that rapid rise and fall of the titer frequently occur, and it is necessary to perform serial tests at frequent intervals, perhaps twice weekly, if one wishes to avoid missing a significant titer.

Of all patients 98.6 per cent revealed the presence in their peripheral blood smear of the typical abnormal lymphocytes characteristic of infectious mononucleosis. All patients fulfilled the established criterion of having at least two of the three classic signs of infectious mononucleosis.

TABLE 1.—*Hepatic Dysfunction in Ninety Patients with Infectious Mononucleosis*

	No. of Patients Tested	No. with Abnormal Values	% with Abnormal Values
Thymol turbidity test	78	63	81.0
van den Bergh test	76	26	33.0
Sulfobromophthalein retention	52	24	46.0
Albumin to globulin ratio	44	5	9.5
Alkaline phosphatase level	38	23	57.0
Cephalin flocculation test	43	34	79.0
Watson test for urobilinogen	60	19	32.0
Cholesterol level	13	2	16.0

Ten of our patients, or 11 per cent, were grossly jaundiced. The thymol turbidity test was performed on 78 patients, in 63 of whom (81.0 per cent) the results were abnormal. The cephalin flocculation test was done on 43 patients, with abnormal results in 34 or 79.0 per cent. Determination of the serum proteins with the albumin to globulin ratio was done in 44 patients, in 9.5 per cent of whom the results were abnormal. Quantitative van den Bergh determinations were made for 76 patients, and 26 (33.0 per cent) showed abnormal elevations. The Watson test for urobilinogen was performed on 60 patients, with 19, or 32.0 per cent, showing abnormal excretion of urobilinogen in the urine. Alkaline phosphatase determinations were made for 38 patients, and 23 (56 per cent) showed an abnormal elevation. The sulfobromophthalein excretion test was performed on 52 patients, and 24, or 46.0 per cent, had abnormal retention. Cholesterol and cholesterol ester determinations were performed on 13 patients, 2 of whom (16 per cent) revealed abnormal values.

A summary of these results shows that one or more abnormal reactions to liver function tests were obtained in 83 of 90 patients, or 90.2 per cent. Two or more abnormal reactions were obtained in 58, or 60.5 per cent. Thirty-two, or 35.5 per cent, exhibited three or more abnormal reactions, and 13 (14.4 per cent) showed four or more abnormal results. Four had five or more abnormal reactions; 2 had six and 1 had seven abnormalities. It should be emphasized that these statistics relate to different function tests, since even those patients listed as having one abnormal reaction may have had this abnormality on five or six repeated occasions. Our impressions as obtained from these test reactions indicate that the thymol turbidity reaction was one of the first to become abnormal and the last to return to normal. Thymol turbidity and cephalin flocculation were the tests with the most frequently positive reactions. The sulfobromophthalein retention was most valuable in patients in whom presence of the disease was doubtful and in determining when liver function had returned to normal. The quantitative van den Bergh reaction was an accurate measure of the degree of clinical or subclinical jaundice and an indication of the clinical improvement, so that it served well as a follow-up test. It is our belief that for screening purposes the thymol turbidity or cephalin flocculation determination, the quantitative van den Bergh and sulfobromophthalein retention tests are adequate, and, if on serial examinations reactions to these tests are negative, one can be sure that a significant hepatic insufficiency is not present. The other tests can be done as confirmatory tests on patients in whom presence of the disease is doubtful.

TABLE 2.—*Duration of Chronic Hepatitis in Seven Patients with Infectious Mononucleosis*

	Duration of Abnormal Liver Function, Wk.						
Patient	H. N.	E. D.	R. T.	J. B.	D. R.	R. Y.	J. H.
Thymol turbidity	85	*	8	23	1	9	*
van den Bergh reaction	81	77	38	23	33	23	3
Sulfobromophthalein retention	*	*	*	*	*	*	127
Albumin to globulin ratio	*	*	*	*	*	*	*
Alkaline phosphatase level	28	68	*	19	73	23	*
Cephalin flocculation	78	*	8	*	*	6	*
Watson reaction for urobilinogen	30	77	74	*	*	*	4
Cholesterol level	85	*	*	*	*	*	*
Icterus index	26	67	*	*	*	*	*

* Negative reaction to test or reaction not rechecked in later stage of the disease.

Follow-up studies have been done on a number of these patients, and in the vast majority of them within three months after onset no evidence of abnormal liver function can be obtained. In 7 patients, however, there were evidences of chronicity or recurrence. One patient still is symp-

tomatic and has abnormal reactions approximately two years after the onset; one patient is asymptomatic but still has 11 per cent retention of sulfobromophthalein. Another patient was mildly symptomatic and had abnormal reactions for thirty-one months. Four other patients have had abnormal reactions for periods varying from five to nine months. It will be necessary to follow these patients for a number of years before an estimate can be made of the incidence of portal cirrhosis. We feel that these 7 cases furnish ample evidence for our contention that vigilance and vigorous management in cases of infectious mononucleosis are needed. Another interesting point is that in these 7 patients the initial symptoms and reactions to liver function tests were not unusually severe and did not give any indication that such an outcome might be expected.

COMMENT

A review of the literature and results obtained with our patients indicates that a large majority of patients with infectious mononucleosis demonstrate abnormal hepatic function on liver function tests. Evidence obtained by punch biopsies of the liver and the autopsy observations on several patients who died from spontaneous rupture of the spleen indicate that the deranged liver function is the result of hepatocellular involvement similar to that seen in infectious hepatitis and is not due, as was previously thought, to extrahepatic obstruction by enlarged glands. These observations indicate that hepatitis with readily demonstrable impairment of liver function is a frequent and probably regular manifestation of infectious mononucleosis. Jaundice occurs in only a small minority of these patients. It is impossible at present to determine how regularly hepatitis occurs in the milder cases, which are undoubtedly frequent but often difficult to recognize with certainty with the diagnostic criteria now available.

It is our belief that all patients for whom a clinical diagnosis of infectious mononucleosis has been established should be considered as having an associated hepatitis and that careful liver function tests, serially repeated if necessary, should be made and active treatment given these patients until such time as the reactions to the liver function tests return to normal. It is our policy to place such patients at absolute rest in bed, employing a high carbohydrate, high protein, moderate fat diet, with administration of vitamin supplements and lipotropic substances as indicated. During periods of anorexia and poor food intake parenteral administration of hypertonic dextrose solutions and amino acids is indicated. After the reactions to liver function tests have returned to normal or appear stabilized at some abnormal level on serial tests, a gradual return to activity is permitted. Such patients should be followed up by screening liver function tests at least several times a year so that it may

be possible in the future to make adequate determinations of the late results of such hepatic insufficiency and its effects on the incidence of portal cirrhosis of the liver.

The cases of recurrent hepatitis contained in this series appear to us to offer an adequate basis for our insistence on vigorous treatment and rigid control of patients with this disease.

SUMMARY

Ninety patients with infectious mononucleosis were studied over a period of three years in regard to the incidence of hepatic involvement. One or more abnormal reactions to liver function tests were obtained in 90.2 per cent of these patients. Seven patients exhibited evidence of chronic or recurrent hepatic involvement for periods varying from five to more than thirty-one months after onset of illness.

The evidence of chronicity affords an adequate basis for insistence on vigorous treatment and control of patients with hepatic involvement in infectious mononucleosis.

EXTRAMEDULLARY PLASMACYTOMA INVOLVING PHARYNX, SKIN AND LYMPH NODES

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EXTRAMEDULLARY plasma cell tumors are comparatively rare. Hellwig [1] analyzed the literature from 1905 to 1942 and found 127 cases, to which he added another. Included in this review were only 2 cases [2] of plasma cell tumors of the skin.

A patient with an unusual condition involving the skin, mucous membrane of the throat and the lymph nodes recently came under our observation. After much deliberation, it was concluded that these lesions represent a rare variant of plasma cell tumor. The case is described in some detail in the following paragraphs.

REPORT OF A CASE

A 53 year old Negro man was admitted to the medical service of Roper Hospital on Jan. 24, 1948, complaining of "lumps on my face and body" first noticed about one year ago.

In 1946 he had had a severe sore throat. There was some lymphadenopathy and his family physician advised and had performed a tonsillectomy.

In March 1947 he noticed small pinkish nodules appearing on his face. These were not painful or pruritic but they interfered with shaving and washing. He thought at the time they were warts. They grew progressively larger and he was admitted to the dermatology clinic of the Roper Hospital. One was excised and was reported by the pathologist to present a picture in conformity with diagnosis of xanthoma tuberosum. The others were removed by cautery.

The lesions recurred and the patient noticed swelling in his neck. In July 1947 he was seen at another hospital where one of the skin lesions was again removed and one of the lymph nodes excised for biopsy. He was discharged from this hospital with his condition unimproved.

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1. Hellwig, C. A.: Extramedullary Plasma Cell Tumors as Observed in Various Locations, Arch. Path. **36**:95 (July) 1943.

2. (*a*) Aragona, P.: Su di un caso di "plasmocitoma," Arch. ital. di anat. e istol. pat. **7**:544, 1936. (*b*) Hedinger, E.: Zur Frage des Plasmocytoms: Granulationsplasmacytom in Kombination mit einem krebsig umgewandelten Schweissdrüssenadenom des behaarten Kopfes, Frankfurt. Ztschr. f. Path. **7**:343, 1911.

About four months before his admission to Roper Hospital in January 1948, he noticed swelling of his axillary and inguinal lymph nodes. At the same time nodules began to appear on the back, anterior wall of the chest, right thigh and left leg. Shortly after the inguinal swelling developed, edema of the penis and scrotum and of the left ankle appeared. He also noted thickening of his speech and some diminution of his hearing, particularly on the left. The lesions at no time had been painful. He stated that he occasionally pinched one off with his fingers when it interfered with shaving.

Fig. 1.—Cutaneous lesions of face and scalp.

His past history revealed a previous admission to the hospital in 1936 because of a perforating gunshot wound of the peritoneal cavity. Wassermann and Kolmer reactions were positive at that time. He received no treatment for syphilis while in the hospital. No tumors of the skin or lymphadenopathy were then recorded. He was discharged after an uneventful recovery.

The family history was essentially noncontributory. He was born in South Carolina in 1895. He had been married twenty-six years and had one child 20 years old. His best weight had been 200 pounds (90.7 Kg.), in 1945, and he had lost about

40 pounds (18.1 Kg.) since that time. In 1940 he received seventy injections for syphilis at a local public health center. With the exception of occasional diffuse headaches and some exertional dyspnea, his previous health had been good.

Physical examination showed a well developed and nourished middle-aged Negro man in no acute distress. His weight was 162 pounds (73.5 Kg.) and his temperature was 98.8 F. Scattered over the body were tumors of varying sizes. They were most numerous on the face and scalp but were present on the head, trunk, right leg and scrotum (figs. 1 and 2). They were pinkish, nontender, soft, pedunculated and easily traumatized with ready bleeding. The lesions varied in size from 0.1 to 3 cm.

Examination of the head showed no bony abnormalities. The ears were normal in appearance. However, diminution of auditory acuity on the left was detected by the watch method. The watch could be heard at a distance of 14 cm. from the right ear but at only 4 cm. from the left ear. The eyes, nose and mouth were essentially normal.

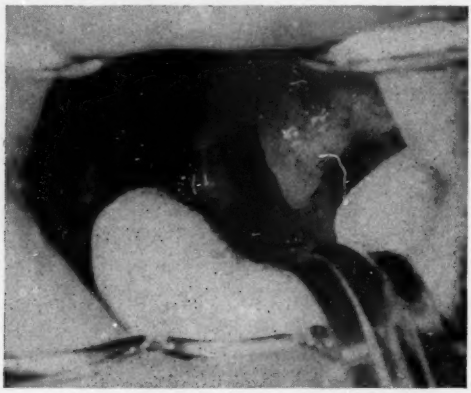

Fig. 2.—Pharynx showing lesion of palate and anterior pillar on right. Uvula is also enlarged and firm, and a nodule is present on the left pillar.

The pharynx showed pronounced hyperplasia of lymphoid tissue, especially on the right. The tonsils had been removed. On the right anterior pillar there was a nodular mass which bore some resemblance to the nodules seen on the skin (fig. 3).

The uvula was thickened and nodular. The voice was thick and muffled. Visualization of the vocal cords revealed no abnormalities. No abnormal pulsations or venous distentions were seen in the neck. The cervical axillary and inguinal nodes were remarkably enlarged, moderately firm and nontender. They were fixed to the skin and were apparently discrete. Some of them seemed to be 3 to 4 cm. in diameter. The epitrochlear nodes were palpable. The lungs were clear and the heart was normal. The blood pressure was 110 systolic and 70 diastolic.

The abdomen showed a large scar in the midline and in the left flank, the result of a gunshot wound in 1936. The liver, spleen and kidneys were not palpable and there was no abdominal tenderness.

The extremities showed no gross changes. Two nodules were present on the lower third of the right tibial area. There was questionable edema of the left ankle. The scrotum and penis were covered with small pinkish white nodules. The penis was edematous. There were no scars or discharges.

A neurologic examination showed no abnormalities.

Laboratory data included the following findings: The hemoglobin concentration was 11 Gm.; the red blood cell count was 3,300,000 and the white blood cell count 5,400 per cubic millimeter, with a differential count of 60 per cent polymorphonuclear leukocytes, 32 per cent lymphocytes, 4 per cent monocytes and 4 per cent eosinophils. The sedimentation rate was 10 mm. per hour (Wintrobe). A

Fig. 3.—Lesions on lower extremity.

preparation of erythrocytes showed no sickling. The reticulocyte count was 1.4 per cent and the thrombocyte (platelet) count was 214,000 cells per cubic millimeter.

The blood urea nitrogen was 15 mg. per hundred cubic centimeters. Blood lipids were found to measure 1.42 Gm. per hundred cubic centimeters. Blood cholesterol ranged from 117 to 140 mg. Serum proteins varied from 10.96 to 13.47 Gm. A representative determination showed 1.86 Gm. of albumin and 9.1 Gm. of globulin. Thymol turbidity was 14.4 McLaughlin units.

Bone marrow studies revealed normal leukopoietic and normal erythropoietic activity. There was no evidence of infiltration by neoplastic or other abnormal

cells. The urine was consistently normal. Numerous examinations for Bence Jones protein gave negative results. Roentgenograms of the chest, skull, long bones, pelvis, spine and hands and feet appeared normal. Cultures of the sputum and of the tissues themselves repeatedly yielded no tubercle bacilli or fungi.

A biopsy specimen was taken of the skin lesions, the tonsil and inguinal and axillary lymph nodes. It was the opinion of the pathologist that the differential diagnosis lay between xanthogranuloma and plasmacytoma. Therefore, the tissue of the skin lesions was extracted and a total fat content of 3.08 Gm. per hundred

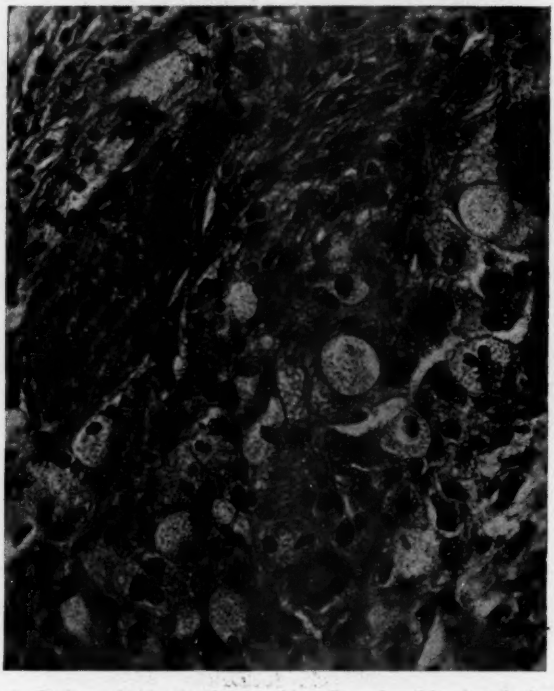

Fig. 4.—Lesions of skin showing xanthic cells and multinucleated giant cells. Hematoxylin and eosin stain; × 650.

cubic centimeters, with cholesterol content of 0.12 per cent, was found. A lymph node was observed to have a fat content of 2.41 Gm. per hundred cubic centimeters. This lipid content was chiefly neutral fat with negligible quantities of phospholipid. The determinations indicated a normal content of fat in these tissues.[3]

An isolated lesion was treated with 1,000 units of roentgen irradiation in divided doses of 200 r each. There was no change in the size of texture of the lesion. It

3. Eckstein, H. C., and Wile, U. J.: Lipid Studies in Xanthoma, J. Biol. Chem. **87**:311, 1930.

was then removed and examined histologically. The structure differed little, if at all, from that of previous sections.

Following this, methyl-*bis*(β-chloroethyl)amine hydrochloride (nitrogen mustard), in doses of 75 mg. given intravenously every other day for fourteen days, was tried, with no response. During the administration of nitrogen mustard, the red blood cell count fell to 2,500,000 per cubic millimeter, the hemoglobin concentration to 9 Gm. per hundred cubic centimeters and the white blood cell count to 5,300. A month after the therapeutic dose of nitrogen mustard was given, the red blood count was 2,200,000 cells, with 7.5 Gm. of hemoglobin and 4,400 white blood cells. The differential count revealed 74 per cent polymorphonuclear leukocytes, 16 per cent lymphocytes and 10 per cent monocytes.

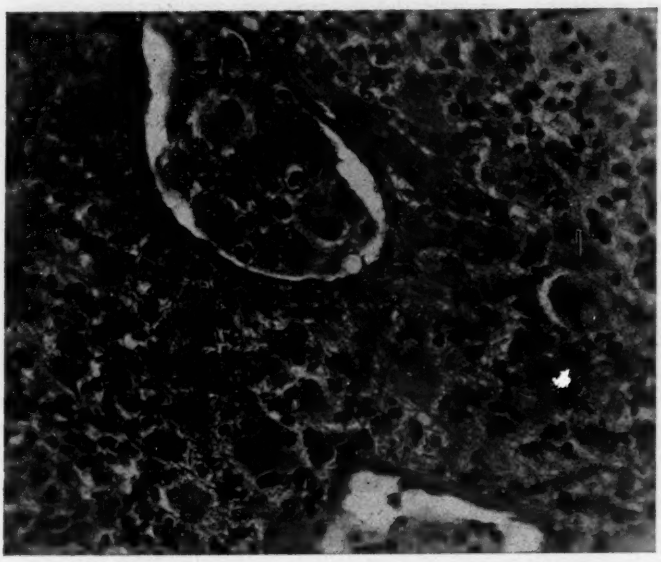

Fig. 5.—Section of skin showing histiocytes, lymphocytes, plasma cells and polymorphonuclear leukocytes. Note dilated blood vessels containing similar cell groups. Hematoxylin and eosin stain; × 650.

The patient was discharged to the outpatient clinic after three months' hospitalization. The lesions were essentially unchanged.

Four weeks later a few small new lesions had appeared on his face, but his hearing had greatly improved and a watch could be heard at equal distances from both ears.

Two months after his discharge he returned again with severe scrotal edema, thought to be due to lymphatic obstruction in the inguinal and femoral areas from infiltration by the plasmacytoma process. Use of a suspensory and restriction of walking and standing notably reduced the edema.

Four months after his discharge tissue chemistry determinations on the lesions were repeated, and a content of 2.08 per cent lipid, with no phospholipid, was observed.

The specimen removed on his first visit to the dermatology clinic in 1947 consisted of a 1 cm. portion of skin with a central pink nodular elevation, measuring 8 mm., having an intact surface and a margin of dark pigmented skin. On section the nodule was poorly defined and grayish tan. Several sections showed ill defined nodular masses of histiocytes. These had a large moderately reticulated nucleus, a prominent nucleolus and varying amounts of pale eosinophilic cytoplasm, some of which showed definite foaming and vacuolation. These cells bore a strong resemblance to the swollen endothelial cells lining small blood vessels in the area. Mitotic figures were easily demonstrated. Scattered irregularly through these nodules and especially prominent about their peripheries were numbers of leukocytes. Plasma cells were especially prominent, and in some areas solid sheets of

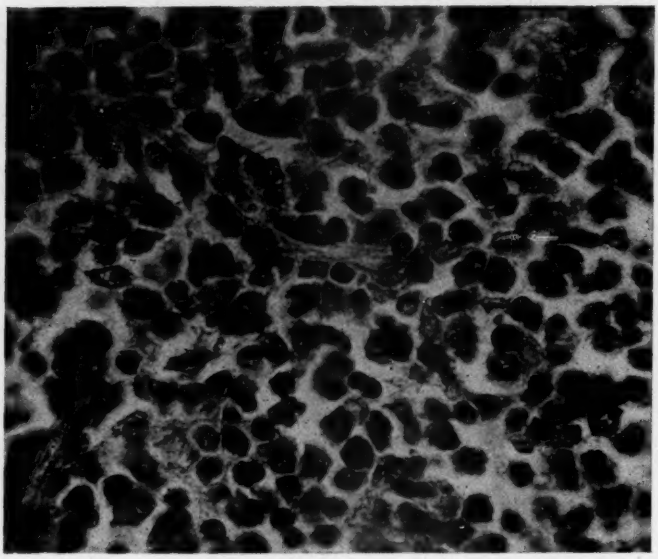

Fig. 6.—Section of lymph node showing prominent plasma cell infiltration. Hematoxylin and eosin stain; × 650.

such cells occupied the complete microscopic field. Eosinophilic Russell's bodies were easily seen. Polymorphonuclear leukocytes were not uncommon, many showing degenerative changes. Eosinophils of stab cell and bilobular type were present in varying numbers and an occasional multinucleated giant cell was seen. The histiocytes were phagocytic and the cytoplasm of such cells contained cellular debris, especially degenerating polymorphonuclear cells. The epidermis was elevated and atrophic, while skin appendages were missing from the nodules themselves.

The clinical diagnosis of xanthoma tuberosum was felt to be confirmed.

The biopsy specimen removed on the patient's admission to the hospital in 1948 consisted of a skin nodule similar to the one first removed. A lymph node about 1.3 cm. in diameter was also removed. It was composed of firm, mottled grayish

tan tissue. These sections of the skin (figs. 4 and 5) were quite similar to the first. The nodular configuration was more evident, many of the nodules being the size of and having a superficial resemblance to miliary tubercles. The histiocytes showed larger and more reticulated nuclei, more mitotic figures and much more phagocytic activity, as evidenced by cell debris and conspicuous vacuolation. Eosinophils were not as numerous but there were many giant cells. Increased fibroblastic activity was evident. The lymph node (figs. 6 and 7) was almost obliterated by nodular masses comparable to those previously described. Plasma cells were especially conspicuous and Russell's bodies were easily observed. Lymph node architecture appeared to be destroyed by infiltration, the remants showing no evidence of compression. There was a variable collagenous stroma which seemed unrelated to the original lymph node.

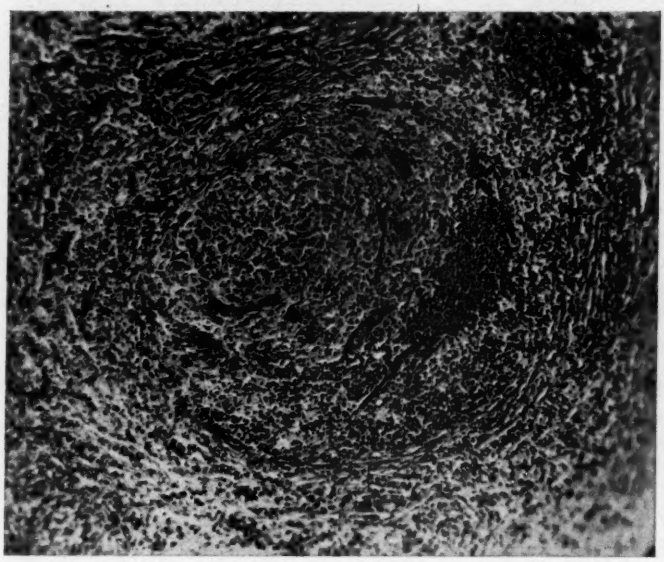

Fig. 7.—Section of lymph node showing nodular granulomatous area with small zone of normal lymphoid structure at one edge. The central cells are largely histiocytes and the peripheral cells largely plasma cells. Hematoxylin and eosin stain; × 150.

A portion of the pharyngeal nodule was then removed. Histologically it appeared to consist of pharyngeal type tissue with a distinct increase in the amount of fibrous stroma, largely of collagenous type. Large numbers of plasma cells with occasional Russell's bodies were scattered through the section, with no apparent attempt at nodular or other characteristic configuration. There were distorted vascular spaces, many having swollen endothelial cells, some of which closely simulated the scattered phagocytic histiocytes. Polymorphonuclear leukocytes were not demonstrable.

An isolated nodule treated with 1,000 r of roentgen irradiation showed no clinical improvement. It was removed and examined histologically. There were a

variable fibroblastic activity, increased numbers of polymorphonuclear leukocytes with a relative decrease in eosinophils and an increase in vacuolation and foaming of the histiocytes. The architecture was generally looser and less definitely nodular than usual. This could be due to strangulative changes which the pedunculated lesions sometimes evidenced.

The lesions revealed no clinical improvement following nitrogen mustard therapy. Histologic examination disclosed no material or determinable changes from the appearance on the first biopsy.

Special stains, including nile blue sulfate and scarlet red preparations for fat, were used. The nile blue sulfate showed the vacuoles in foam cells as blue staining, while peripheral free fat stained orange. The scarlet red stain showed the foam cells to contain orange-staining material. Reticulum stains did not reveal any significant increase in fibers. Other stains, including bacterial and acid-fast stains, were done without significant results.

Because of the pathologic picture the differential diagnosis lay between xanthogranuloma and plasmacytoma. Consultation with pathologists elsewhere resulted in divided opinions. The normal lipid determination led Dr. Thannhauser [4] to state that this was probably not xanthogranuloma but plasmacytoma.

COMMENT

The clinical picture and original studies of the histologic structure led to the conclusion that this condition represented an eosinophilic xanthogranuloma showing the proliferative stage. However, plasmacytoma was considered, and when repeated normal values for blood cholesterol and a normal fat content of the tumor were demonstrated it was concluded that this was an unusual form of extramedullary plasmacytoma.

The site of predilection for extramedullary plasma cell tumors is the upper part of the respiratory tract.[1] A careful review of the history of the present patient indicates that his first complaint was an unusual swelling in the throat with lymph node involvement. His tonsils were removed but no histologic study was done.

So far as we have been able to discover, there have been only the 2 cases of plasma cell tumor involving the skin cited by Hellwig.[1] Hedinger [2b] described an unusual tumor of the skin of the scalp, half of which was composed of plasma cells; the other half was apparently an adenocarcinoma originating in a sweat gland. Cervical lymph nodes removed at the time showed only metastatic carcinoma. Aragona [2a] removed a tumor from the skin of the neck of a 6 year old girl. The tumor was composed of plasma cells and had not recurred five years after its removal. Hellwig [1] cited 4 cases of plasma cell tumor originating in the lymph nodes and 9 of plasma cell tumors of the air passages associated with enlargement of the regional lymph nodes.

It is known that the clinically noncancerous stage of plasmacytoma may persist ten years or more, but ultimately the process tends to

4. Thannhauser, S. J.: Personal communication to the authors.

become generalized, whether by metastasis or multicentric origin. No therapeutic measure is known to have prevented a fatal outcome if applied after the tumor has involved either the skeleton or the lymph nodes.[1] Irradiation frequently produces a clinical cure if no metastasis has taken place. For diagnostic purposes, as well as for planning future therapy, an isolated lesion in this patient was subjected to 1,000 r of roentgen irradiation, but no change in either the gross or the microscopic picture took place.

Following this, treatment with one of the nitrogen mustards was tried, with some subjective improvement but with no objective changes either clinically or microscopically. At present he is receiving urethane treatment under the supervision of another group of physicians, but as yet no startling changes have resulted that could be determined at the time of his last visit to our clinic.

SUMMARY

An unusual case of extramedullary plasmacytoma involving the pharynx, skin and mucous membranes is presented.

CARDIOPATHY IN FRIEDREICH'S ATAXIA (SPINAL FORM OF HEREDITARY SCLEROSIS)

Review of Literature and Analysis of Cases of Five Siblings

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IT IS REMARKABLE that up to 1948 there had been no publication by American investigators on any aspect of the cardiopathology of Friedreich's ataxia (spinal form of hereditary sclerosis). At this time a report by Ellwood appeared in which he described 2 patients having Friedreich's disease, one of whom died seemingly of coronary occlusion and the other in congestive failure. Recently, a second report has appeared (Hejtmancik and others) in which descriptions of 2 patients with Friedreich's disease are presented, both having striking electrocardiographic changes and apical diastolic murmurs.

REVIEW OF LITERATURE

In Friedreich's original report (1863 *a*) of 6 patients, one had experienced palpitation, dyspnea and paroxysmal auricular tachycardia, while 2 others had complained of frequent palpitation. On physical examination 5 were reported as showing no cardiac abnormality, while 1 had cardiomegaly and an apical systolic murmur. Postmortem examination of this patient revealed hypertrophy of the left and right ventricles, thickening of the aortic valve and thickening and calcification of the mitral valve. The myocardium was reported as being normal in color and consistency. Postmortem studies of 2 other patients showed some fatty degeneration of the myocardium and ventricular thickening on the left. It is noteworthy that each of the 3 patients in this series who came to autopsy died of an acute illness, in all probability typhoid. In subsequent articles, Friedreich (1863 *b*; 1876; 1877) described 3 more patients, none of whom had symptoms or signs of cardiac disease. One of his original patients displayed a persistent tachycardia which prompted him cautiously to discuss cardiac arrhythmias and to suggest that these might be secondary to involvement of the medulla oblongata. When this patient came to postmortem observation, a detailed examination of the central nervous system revealed no pathologic involvement in

the medulla or bulbar nuclei (Schultze). When another of this group came to postmortem study, fatty degeneration of the heart was noted. Friedreich tended to minimize these cardiovascular manifestations and observations. The same may be said for Ormerod and Bury, although both these authors did comment on the occurrence of systolic murmurs in their patients.

It remained for Pitt in 1887 to make the following astute observation: "Hitherto sufficient attention has not been drawn to the condition of the circulatory system [in Friedreich's disease] and yet on looking through the records it is astonishing to see how often cardiac failure has been noticed." Furthermore, in this paper Pitt gave a detailed follow-up report of one patient with Friedreich's ataxia in whom there was no evidence of cardiovascular abnormality initially. Seven years later on readmission this patient was observed to have cardiac enlargement, accentuation of the pulmonary second sound, an apical systolic murmur, tachycardia and chronic passive congestion. Later cardiac irregularity appeared. On subsequent cardiac examination it was reported that "at the apex, a bruit, doubtfully presystolic [is] occasionally audible." After sudden death, postmortem examination showed cardiac hypertrophy and dilatation. Two of the aortic valve cusps were seen to be adherent, slightly irregular and calcified. The myocardium showed granular degeneration, fibrosis and, in some areas, infiltration with "small cells." In addition, examination of the upper extremities revealed a "widely distributed obliterative endarteritis of the smaller vessels." The coronary vessels were not mentioned. Sclerosis of both the lateral and the posterior columns and a "congenitally small" cord were noted. He summarized by citing five points in favor of Friedreich's disease being a "systemic" disorder and concluded that it was not unreasonable to believe that the congenitally small cord, as well as the location of the degeneration in the central nervous system, was a consequence of "an inherited tendency to general early vascular degeneration."

Regardless of whether or not Pitt's formulation of the pathogenesis of Friedreich's disease is correct, he is deserving of credit since he was the first investigator to focus attention on the cardiac manifestations of the disease and to relate these to the involvement of the central nervous system. His was also the first report of "myocarditis" observed in Friedreich's disease, unassociated with an acute terminal illness. The only contributions in addition to Pitt's relative to the cardiopathy associated with Friedreich's disease that have appeared in the literature in the intervening sixty-five years have been those of the French workers after the advent of the electrocardiograph.

In 1932 Guillain and Mollaret reported on the "cardiobulbar syndrome" as a frequent cause of death in Friedreich's disease. Two patients

described in detail displayed symptoms of cardiac disease, including palpitation, dyspnea and tachycardia, intermittently during the course of their neurologic disorder. In both persons systolic murmurs were heard. Repeated electrocardiographic tracings of one patient showed a flattened T_1 and inversion of T_2 and T_3. The electrocardiogram of the other showed a P-R interval of 0.19 second, slurring and notching of the QRS complexes and a diphasic T_3. In the necropsy report no comment was made about any myocardial lesion in either patient. These authors stressed arrhythmias rather than other electrocardiographic alterations, such as changes in the T waves. Bulbar involvement was favored as an explanation for the cardiac and respiratory arrhythmias, as well as the dysphagia and transient (visceral) vasomotor disturbances, noted in these patients.

Two years later the same authors (Guillain and Mollaret, 1934) reported on a patient with Friedreich's disease having normal results on cardiac examination and electrocardiographic study in 1931 but showing definite electrocardiographic alterations in 1934. These included auricular extrasystoles, Pardee-like curves in leads I and II and a negative T_3. Since this patient was only 19 years of age, it was the authors' opinion that coronary insufficiency could not be responsible for these changes. Rathery and his associates also reported on a patient having Friedreich's ataxia with similar clinical and electrocardiographic findings. These were attributed to bulbar involvement, and the authors stated that the appearance of such changes made the prognosis ominous. Laubry and Lian (cited by Rathery and others) concurred in this opinion. In 1936 Laubry and Heim de Balsac reported on 2 patients with Friedreich's disease, one of whom was 19 and the other 30 years of age when palpitation, tachycardia and extrasystoles were noted. In one patient the electrocardiogram showed inverted T waves in leads II and III, and in the tracing for the other patient Pardee T waves appeared which were said to be similar to those in "coronary disease." Injection of radiopaque material into the coronary vessels revealed no abnormalities of the coronary vascular bed on roentgenologic examination. They concluded that the electrocardiographic changes observed in Friedreich's disease were due to myocardial involvement rather than to coronary lesions, and they were of the view that this was on a neurologenic basis, inasmuch as definite myocardial changes had not been consistently seen on postmortem examination.

Desbach and his co-workers described a patient with Friedreich's disease with a history of "heart trouble" antedating the onset of neurologic symptoms. Physical examination revealed cardiomegaly and a double mitral murmur. Orthodiascopic examination supported the clinical impression of mitral valve disease. An electrocardiogram

showed diphasic T_1 and T_3. The authors stated their opinion that this was indicative of a myocardial lesion and that the mitral involvement was probably coincidental.

Debré and his collaborators reported the case of a boy with Friedreich's disease, kyphoscoliosis, a systolic murmur over the heart and inversion of T_2 and T_3 in the electrocardiogram. It was also noted that the child's father had kyphoscoliosis, Friedreich's deformity of the foot and electrocardiographic changes consisting of a deep Q_3 and an inverted T_3.

Van Bogaert and van Bogaert reported on a study of 8 patients with Friedreich's ataxia, among whom were 2 sets of siblings and 3 "isolated" patients. The first set of siblings were 7, 11 and 17 years of age. The youngest and oldest were noted to have a "third protodiastolic bruit" on effort. The 11 year old child showed no cardiac abnormality. The electrocardiogram of the 17 year old patient contained prominent Q waves in leads I and II; T_1 was erased, and T_2 was faintly negative. The 11 year old child had electrocardiographic changes consisting of a prominent S wave in lead III and negative T_2 and T_3. The youngest child's electrocardiogram revealed only auricular extrasystoles in lead III. The second sibling study was of 2 sisters, aged 33 and 36. One had a "third sound protodiastolic." The sisters' electrocardiograms were similar. T_1 and T_2 were diphasic, and, in one, T_3 was faintly negative. In the 3 "isolated" patients, cardiac examination was not revealing but electrocardiographic studies showed a prominent S wave in lead I, low T_2 and negative T_3. The second showed left-sided preponderance with normal T waves. The electrocardiogram was normal in the third. In their discussion, these authors cited the frequency of arrhythmias in their series and emphasized alterations in the T waves. They also observed that the cardiac manifestations were more outspoken when the neurologic manifestations were pronounced. They proposed that the T wave changes were due to a "deviation of normal physiochemical processes accompanying the contraction of the heart muscle."

Evans and Wright reported on 38 patients having Friedreich's disease who were studied from a physical, orthodiascopic and electrocardiographic standpoint. Only one person had an abnormal pulse and this was due to heart block. Murmurs were not heard. Lateral displacement of the apex beat, which was demonstrated in a few of the patients, was attributed to scoliosis, yet slight enlargement of the left ventricle was proved by orthodiascopic study in 8 of them. Twelve subjects had "abnormal" electrocardiograms. Three showed a T_1 type pattern of cardiac infarction (Parkinson-Bedford); 3 showed T_3 type, and 5 showed a low or inverted T wave in the three limb leads. Ten subjects had electrocardiographic tracings displaying "minor" changes which, in the authors' opinion, might be secondary to the deformity of the chest,

a prominent feature in some of their patients. These changes consisted of deep S waves in leads I and II in 5 patients and deep S waves in leads II and III in the other 5. The remaining 16 electrocardiograms were normal. These authors pointed out that involvement of the nervous system as a whole was greatest in those patients with abnormal electrocardiograms. They also observed the striking association of a positive family history (one or more relatives having Friedreich's disease) with abnormal electrocardiographic changes. They mentioned that affected members of the same family tended to show the same electrocardiographic alterations. They concluded by stating that Friedreich's disease is "as much an affection of the heart as of the nervous system."

Four persons with Friedreich's ataxia were studied from a clinicopathologic standpoint by Russell. Tachycardia was present in each of them. In only one, however, was there a systolic murmur. Necropsy examination showed hypertrophy of the myocardium and microscopic changes consistent with chronic myocarditis in all 4 patients. Examination of the central nervous system revealed no changes in or about the vagal nuclei, and this author concluded that the myocarditis was probably toxic in origin.

In Ellwood's article one of the 2 patients had "leakage of the heart" which antedated the onset of neurologic manifestations. This patient had cardiac enlargement, a precordial systolic murmur and intermittent irregularity of the pulse. There was no electrocardiogram. Postmortem examination showed enlargement of the left ventricle, scarring and slight nodular thickening of the mitral valve, "old scarring" of the myocardium and a clot in the left coronary ostium. The second patient had paroxysmal auricular tachycardia which was confirmed by electrocardiogram. Unfortunately, no comment was made concerning the results of physical examination of the heart. Postmortem examination revealed cardiac enlargement and diffuse interstitial fibrosis of the myocardium. It is noteworthy that, in addition to the arrhythmias, the electrocardiogram in this patient showed slight inversion of T_4 and prominent S waves in leads II and III. Ellwood's comment was confined to the fact that cardiac complications were present in these 2 patients and that these complications may begin at an early age, with death resulting.

The most recent report, of 2 patients having Friedreich's disease with cardiac complications, was made by Hejtmancik, Bradfield and Miller. The first patient had auricular fibrillation, cardiac enlargement and an apical middiastolic murmur. The electrocardiogram for this patient showed supraventricular ectopic beats, right axis deviation and definite evidence of myocardial damage. It is noteworthy that the last was manifested by a flat T_1 and inversion of T_2 and T_3. Necropsy study revealed cardiac enlargement with hypertrophy of the left ventricle and

a diffuse interstitial fibrosis of the myocardium. The second patient had premature contractions and a short, low-pitched presystolic murmur at the apex. Again it is noteworthy that the pronounced "alterations" of the electrocardiogram in this patient were inversion of T_1, T_2 and T_3. The authors commented on the diastolic murmurs heard in their subjects and cited similar examples from the literature in support of this observation. Although they noted that a patient of Pitt had a "bruit doubtfully presystolic," they failed to mention that this subject originally was reported to have a systolic murmur at the apex and that later Pitt made the comment, "at the apex, a bruit doubtfully presystolic [is] occasionally audible." They referred to the diastolic murmur heard in a patient of Desbach and his associates, but it is pertinent that this patient had a systolic as well as a presystolic murmur and that orthodiascopic examination confirmed the clinical impression of disease of the mitral valve. From the description offered by van Bogaert and van Bogaert the "protodiastolic" element noted in 3 of their subjects could have been a third heart sound rather than a true diastolic murmur, as suggested by Hejtmancik and co-workers. These authors concluded with the statement that a thorough cardiac study is indicated in patients with Friedreich's disease.

ANALYSIS OF CASES

1. *History.*—The present analysis of cases concerns 5 siblings, 3 of whom were first seen by members of the Neuropsychiatric Service of the Wisconsin General Hospital and whose condition was diagnosed as Friedreich's ataxia. They were referred to the cardiology service because murmurs had been noted on routine physical examination and the possibility of rheumatic heart disease had been raised. On the basis of the remarkably similar cardiac findings in these 3 children, the 2 other siblings, as well as the parents, were subsequently examined by members of both the cardiology and the neuropsychiatric services.

The diagnosis of Friedreich's ataxia in each instance was made without reservation on the basis of the characteristic neurologic findings demonstrated in the 5 children. The progression of the disease was most apparent in the eldest girl, aged 14, and least so in the youngest sibling, a girl aged 8. A 10 year old boy, an 11 year old girl and a 13 year old girl showed neurologic disturbances in direct relation to their ages. The youngest child showed unsteadiness of gait, general hypotonia, absence of deep tendon reflexes, intention tremor in the upper extremities and general clumsiness and ataxia on coordinated and finer movements in both the upper and the lower extremities. A definite pes cavus was present, and a tendency to plantar flexion of the distal phalanx of the great toes, with a beginning contracture of the proximal phalanx of the left great toe, was noted. The 3 older girls all showed the characteristic Friedreich deformity of the foot. The eldest girl had such severe ataxia and hypotonia that she was practically incapable of locomotion. There was a definite scanning dysarthria present, as well as conspicuous kyphoscoliosis which none of the younger siblings showed.

It was impossible to elicit a family history of any type of neurologic disorder from either parent. The family history in regard to cardiovascular disorders revealed that the paternal grandfather had died of "coronary thrombosis" at the

age of 66; the maternal grandfather had died of a "stroke" at the age of 70, and the maternal grandmother had died of a "weak heart and flu" at the age of 70. The children's mother had had "growing pains" as a youngster and scarlet fever at the age of 27. Since this time she had been known to have a murmur.

Each of the children had a normal birth and delivery, and their development had been "normal" up to the approximate age of 7 or 8 years, at which time the first evidences of ataxia were noted in each of the siblings. They all had had measles, chickenpox and scarlet fever, the last at the same time their mother had it. None of the children offered any cardiac complaints, nor were the parents cognizant of any cardiac symptoms or signs in the children.

2. *Cardiac Examination.*—Case 1.—M. A. T. was a girl 8 years of age. Her pulse was regular; the rate was 96. The blood pressure was 110/60-50. The apical impulse was visible and palpable in the fourth and fifth left interspaces in the midclavicular line. Slight apical and precordial heaving was noted. The heart was slightly enlarged to the left on percussion. The apical sounds were normal in all areas. The pulmonary second sound was louder than the aortic second sound. There was a harsh, grade IV (Levine's classification) systolic murmur heard over the entire precordium, equally loud at the base and apex, well transmitted to the left axilla and persisting on deep inspiration. The lungs were clear; the abdomen was normal, and there was no edema present.

Case 2.—L. T. was a 10 year old boy. His pulse was regular; the rate was 100. The blood pressure was 110/70-60. The apical impulse was visible and palpable in the fourth left interspace 5 mm. within the midclavicular line. The heart sounds were normal, and the pulmonary second sound was louder than the aortic second sound. A loud venous hum was heard over the upper part of the precordium. There was a slightly harsh grade II systolic murmur in the third, fourth and fifth left interspaces, maximum at the apex and faintly heard in the left axilla. This murmur decreased to grade I on deep inspiration. With the child recumbent the venous hum disappeared; the systolic murmur became rougher and louder, grade III, and was maximum in the third left interspace. With deep inspiration the murmur decreased to grade I. The lungs were clear; the abdomen was normal, and there was no edema.

Case 3.—R. J. T. was a girl 11 years old. Her pulse was regular and its rate 84. The blood pressure was 120/65-60. The apical impulse was visible and palpable in the fourth interspace 1 cm. inside the midclavicular line. The heart sounds were normal, and the pulmonary second sound was louder than the aortic second sound. A slightly harsh, blowing grade III systolic murmur was heard maximally in the second and third left interspaces at the sternal border. The murmur was transmitted down over the precordium to the apex and to the left axilla. The murmur decreased to grade II on deep inspiration at the pulmonary area but entirely disappeared at the apex. With the child in the recumbent position the systolic murmur was slightly louder and harsher at the pulmonary area. The murmur persisted at the base but disappeared at the apex on deep inspiration. The lungs were clear; the abdomen was normal, and there was no edema present.

Case 4.—L. A. T. was a girl aged 13. Her pulse was regular, its rate 88. The blood pressure was 125/60-55. The apical impulse was visible and palpable in the fourth interspace 1 cm. outside the midclavicular line. There was slight apical heaving. The apical sounds were normal, and the pulmonary second sound was louder than the aortic second sound. There was a moderately harsh, blowing grade III systolic murmur heard maximally at the pulmonary area and transmitted down along the sternum to the apex and to the left axilla. The

murmur decreased but did not disappear on deep inspiration and became grade IV on forced expiration. A short, harsh systolic murmur was heard over the vessels of the neck. With the child recumbent a systolic thrill was felt in the third left interspace. The systolic murmur became louder, grade IV, and was maximal over the third left interspace. The murmur decreased to grade II on deep inspiration. The lungs were clear; the abdomen was normal, and there was no edema present.

CASE 5.—S. L. T., 14 years of age, was the eldest girl. Her pulse was regular and the rate 96. The blood pressure was 110/70-60. The apical impulse was visible and palpable in the fifth interspace 1.5 cm. inside the midclavicular line. The heart sounds were normal, and the pulmonary second sound was louder than the aortic second sound. A slightly harsh grade III systolic murmur was heard with maximum intensity in the second and third interspaces just to the left of the sternum. This murmur was transmitted down over the precordium to the apex and faintly to the left axilla; it decreased to grade I on deep inspiration at both the apex and the base. With the patient in the recumbent position, a fine systolic thrill was felt in the third left interspace and the systolic murmur at this area increased to grade IV. The murmur decreased to grade II over the pulmonary area and was only faintly heard over the apex on deep inspiration. The lungs were clear; the abdomen was normal, and there was no edema present.

CASE 6.—The mother was 34 years of age. The pulse showed sinus arrhythmia, with a rate of 76. The blood pressure was 130 systolic and 85 diastolic. The apical impulse was palpable in the fifth left interspace 2 cm. inside the midclavicular line. There was a short presystolic thrill at the apex. The first apical sound was accentuated. The pulmonary second sound was louder than the aortic second sound. There was a slightly harsh, blowing grade III systolic murmur heard along the left sternal border and at the apex, transmitted to the left axilla and persisting on deep inspiration. There was a short grade I middiastolic murmur heard in the third left interspace during quiet respiration only, disappearing on deep inspiration and full expiration. With the woman recumbent the presystolic thrill at the apex was more pronounced, the systolic murmur was unchanged, but no presystolic or diastolic murmur was heard. The lungs were clear; the abdomen was normal, and no edema was present.

CASE 7.—The father was aged 40. The pulse was regular, with a rate of 80. The blood pressure was 130 systolic and 70 diastolic. The apical impulse was palpable in the fifth left interspace 1.5 cm. inside the midclavicular line. The heart sounds were normal. There was a short, slightly harsh grade I systolic murmur in the third left interspace at the sternal border, which disappeared on deep inspiration. In the recumbent position his systolic murmur became slightly louder and more blowing, grade II, but it still disappeared completely on deep inspiration. The lungs were clear; the abdomen was normal, and there was no edema present.

In summary, it is of interest that the auscultatory findings were remarkably similar in the 5 siblings, although these findings were not characteristic of any definite organic cardiac lesion.

3. *Orthodiascopic Examination.*—CASE 1.—The aorta was denser than normal. The pulmonary artery was slightly prominent but not grossly dilated. The apical contour was blunt and rounded. The heart size was at or slightly above the upper limits of normal. There was no evidence of rheumatic valvular disease.

CASE 2.—The aorta, as in M. A. T., was increased in density and the pulmonary arch was slightly prominent. Again the apex was somewhat blunt and rounded. Otherwise, the heart was normal in size and shape with no evidence of rheumatic valvular disease.

CASE 3.—The aorta was increased in density. The pulmonary arch was slightly prominent. The cardiac contour was normal, but there was moderate generalized enlargement of the heart shadow. No evidence of rheumatic valvular disease was demonstrated.

CASE 4.—The aorta was increased in density. The pulmonary arch was slightly prominent. The cardiac contour was normal. The esophagus on filling with barium sulfate solution was slightly displaced at the level of the left auricle in the right anterior view. There was no cardiac enlargement.

CASE 5.—The aorta was increased in density. The pulmonary arch was moderately prominent. The esophagus when filled with barium sulfate solution was moderately displaced at the level of the left auricle in the right anterior oblique and

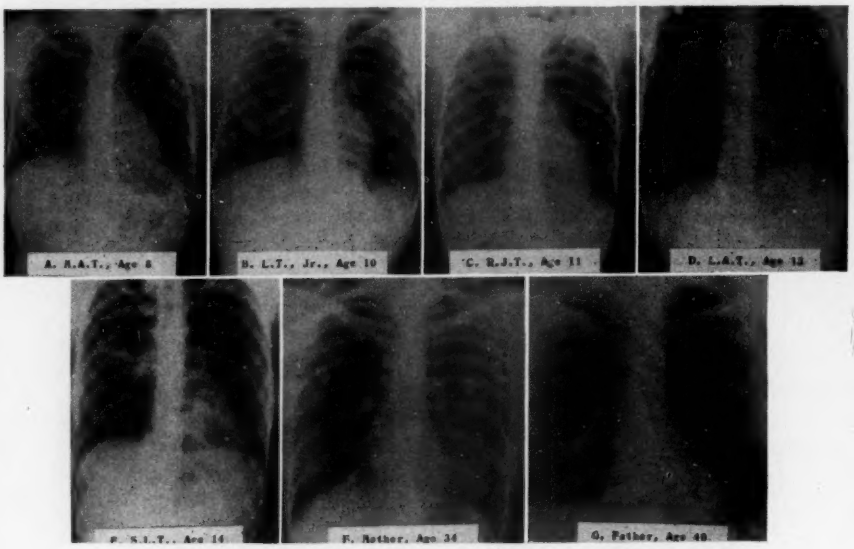

Fig. 1.—Roentgenograms of 5 siblings having Friedreich's ataxia with cardiac manifestations and of their father and mother.

frontal views. The cardiac contour was otherwise normal and the heart was not enlarged.

CASE 6.—Except for slight prominence of the pulmonary arch and slight dilatation of the left auricle, the cardiovascular shadow was normal in size and shape.

CASE 7.—The aorta was slightly increased in density for a man of his age; otherwise, the cardiovascular shadow showed no abnormality.

In summary, it is of interest that the aorta was increased in density and the pulmonary arch was slightly prominent in all 5 siblings. The father also exhibited increased density of the aorta. There was evidence of cardiac hypertrophy or dilatation in 3 of the children but none in the remaining 2 siblings.

Photographs of the miniature roentgenograms of the chest of the 5 siblings and their parents are reproduced in figure 1. The size and contour of the heart of each of the subjects, however, were determined by orthodiascopy.

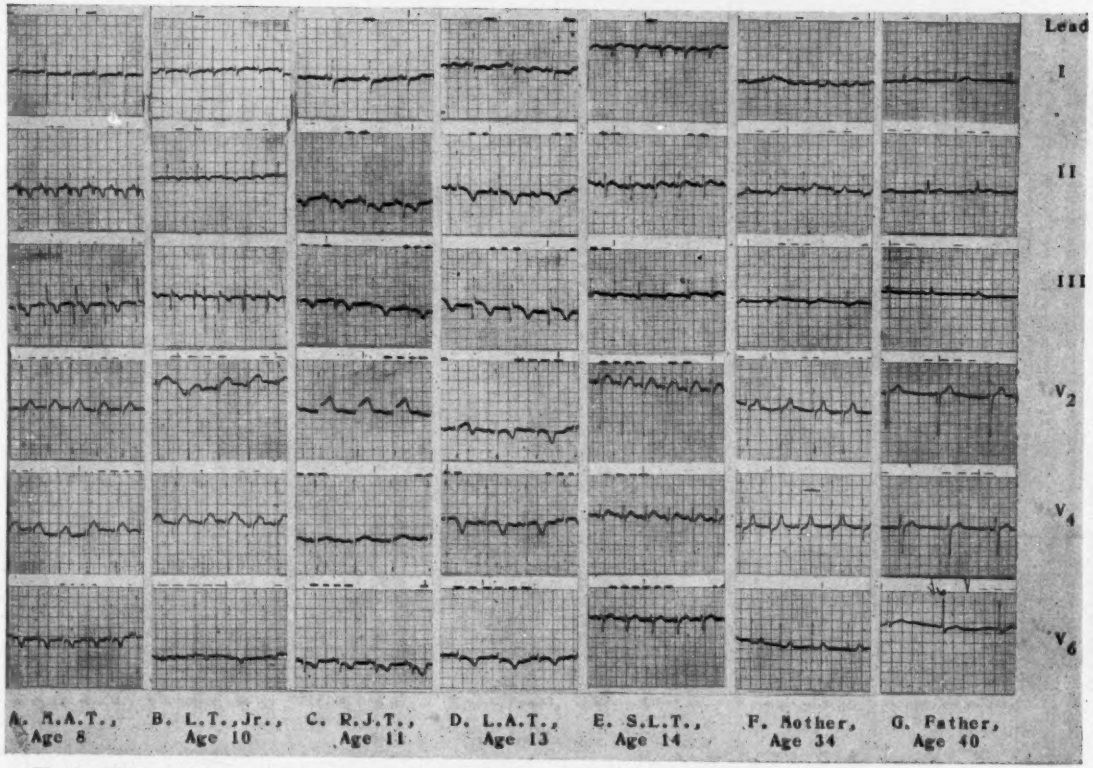

Fig. 2.—Electrocardiograms of 5 siblings having Friedreich's ataxia with manifestations of cardiac disease and of their father and mother.

4. *Electrocardiographic Study.*—Case 1.—As reproduced in fig. 2 *A*, this child's tracing showed tachycardia and sinus arrhythmia, with a rate of 105 to 140. The tracing also revealed right axis deviation, peaked P_2, deep Q_3 which did not alter on deep inspiration, slight upward convexity of the RS-T segment in lead V_6, low and inconstantly diphasic T_1, inversion of T_3, T_5 and T-V_6 and notching of T-V_5 and T-V_4. The P-R interval measured 0.1 second and the QRS complex 0.06 second.

Case 2.—This electrocardiogram, reproduced in figure 2 *B*, showed tachycardia and sinus arrhythmia. The rate was 100 to 125. Left axis deviation, small Q-V_6, small S_1, slight depression of RS-T_1, slight elevation of RS-T_3, low T_1 inverted T_3, T_5 and T-V_6, broadened T-V_2 and notched T-V_4 were present. The P-R interval measured 0.12 second and the QRS complex 0.06 second.

Case 3.—This electrocardiogram, reproduced in figure 2 *C*, showed normal rhythm, with a rate of 80 to 85, peaked P waves in leads, I, II, V_3, V_4 and V_6, deep Q_3, small Q waves in leads II and V_6, prominent S_1, upward convexity of the RS-T segments in leads II, III and V_6, high take-off of RST-V_2, low T_1, low T-V_4 and inversion of T_3, T_5 and T-V_6. The P-R interval was 0.12 second. The QRS complex measured 0.07 second.

Case 4.—This electrocardiogram, reproduced in figure 2 *D*, showed normal rhythm, with a rate of 70 to 80. Peaked P_1 and P_3, prominent Q_3, small S_1, depressed RS-T_1, upward convexity of RS-T segments in leads II, III, V_3 and V_6, slight elevation of RS-T_3, elevated RS-T_6, a T_1 which was diphasic but chiefly inverted and inversion of T_3, T_5, T-V_2, T-V_4 and T-V_6 were also noted. The P-R interval measured 0.16 second and the QRS complex 0.07 second.

Case 5.—This electrocardiogram, reproduced in figure 2 *E*, showed tachycardia. The rate was 125 to 130. Right axis deviation, peaked P_2 and P_3, small Q_3, prominent S_1 and S_3, upward sloping of RS-T_1 and RS-T_3, with the latter slightly elevated, slightly elevated RS-T_3, upward sloping of RS-T segments in leads V_3 and V_4, low T_1 and T_3, slight inversion of T_3, broadening of T-V_3 and T-V_6 and slight peaking of T-V_4 were present. The P-R interval was 0.12 second and the QRS complex 0.07 second.

Case 6.—This electrocardiogram, reproduced in figure 2 *F*, showed sinus arrhythmia, with a rate of 90 to 105. It disclosed a small Q_3, low QRS_1 and the T waves upright in all leads. The P-R interval measured 0.12 second and the QRS complex 0.06 second.

Case 7.—This electrocardiogram, reproduced in figure 2 *G*, showed sinus arrhythmia. The rate was 55 to 70. A low QRS_1 and QRS_3, with slurring of QRS_3, low T_1 and T_2 and flat T_3 were present. The P-R interval was 0.19 second and the QRS complex 0.07 second.

In summary, it is noteworthy that all the siblings and the father exhibited electrocardiographic alterations involving the T waves. Four of the children showed definite inversion of T waves in leads II, III and V_6. The eldest sibling and the father showed low T waves without significant inversion. A prominent S_1 was present in the tracings of all 5 siblings, to the extent of producing right axis deviation in 2. In the father's electrocardiogram S_1 was present but was less pronounced than in the tracings of the children. Peaked P waves were practically a constant observation in the tracings of the 5 siblings.

COMMENT

Friedreich's ataxia is usually considered to be a relatively rare "neurologic" disease, and until recently the cardiac aspects have received little attention in the American literature. It is obvious from the review of

the American and European literature and the cases herein reported that cardiac involvement is a serious and relatively frequent concomitant of Friedreich's disease. Consequently, it is felt that much greater emphasis and more active investigation should be directed toward this disorder from the standpoint of both organ systems involved, regarding it as a systemic rather than a purely neurologic disease.

In connection with the present analysis of cases, a number of comments seem in order. The systolic murmurs heard on examination of the 5 siblings were strikingly similar. At the onset at least three possible explanations for these murmurs were considered, that they were (1) of functional or "accidental" origin; (2) caused by rheumatic valvular disease, or (3) due to an auricular septal defect, possibly patent foramen ovale. The first explanation was favored from a clinical standpoint and orthodiascopy failed to demonstrate signs indicative of the second or third. The vast majority of murmurs reported in patients having Friedreich's ataxia with cardiac abnormalities were described as systolic and most of these were considered as functional or "nonorganic." In many instances, this was later proved on necropsy. The few valvular lesions seen in patients on postmortem examination undoubtedly were a consequence of rheumatic valvulitis and might well be considered as merely coincidental. It is of interest that even the diastolic auscultatory findings of van Bogaert and van Bogaert and Hejtmancik and his associates were considerd as probably functional. Thus, it seems that from simply an auscultatory standpoint the murmurs noted in patients with Friedreich's ataxia are not in any way diagnostic. Yet, they are important since, if nothing else, they draw the clinician's attention to the possible existence of cardiac lesions.

From an orthodiascopic standpoint, 2 of the persons in the present report showed the blunt, rounded apex characteristically observed in hypertrophy of the left ventricle and 1 had a moderate generalized enlargement of the heart. Again, there is nothing particularly diagnostic about this finding of cardiomegaly, but its presence is certainly of importance, since it is objective evidence of cardiopathy. Of even greater significance, however, might be the fact that the orthodiagram tends to rule out a rheumatic or congenital lesion.

The most striking and consistent changes were noted in the electrocardiogram. The tracings of the 5 siblings reported on showed remarkably similar changes in the T waves when compared both to each other and to those in the literature. This pronounced similarity renders simple coincidence highly improbable. Yet the explanation for the electrocardiographic changes remains unsettled.

A congenital disturbance of the electrical potentials in the myocardium and a "toxic myocarditis" have been suggested by some of the European writers (Debré and others; Desbach and others; Evans and

Wright; Russell; van Bogaert and van Bogaert) to account for the T wave changes described. The basis for these conceptions remains to be proved. Intrinsic coronary vascular disease constitutes another possibility, but the extreme youth of the subjects showing these alterations makes this explanation extremely unlikely. Moreover, the study of Laubry and Heim de Balsac, which demonstrated the integrity of the coronary vascular bed in a patient with Friedreich's ataxia exhibiting the characteristic electrocardiographic changes, would tend to minimize this possibility.

Many of the French investigators were impressed by the arrhythmias encountered in their subjects with Friedreich's ataxia. These were variously attributed to a "cardiobulbar syndrome" (Guillain and Mollaret [1932; 1934]; Laubry and Heim de Balsac; Rathery and others) or a congenital defect of the myocardium (van Bogaert and van Bogaert). The infrequency of demonstrable involvement of the brain stem and the lack of proof of a congenital myocardial defect leave these theories open to question. The arrhythmias described in the literature were largely "ectopic" in type and did not originate primarily in the conduction system. These may have arisen from irritable foci in the myocardium, and it seems logical to assume that these arrhythmias may have been due to the same underlying myocardial disturbance responsible for the changes in the T waves.

Further conjecture regarding this problem is not warranted on the basis of the present study; yet there is every reason to emphasize the real importance and necessity of further investigation relative to this matter, since it would seem that the cardiac abnormalities observed in persons with Friedreich's ataxia are as fundamental and pertinent in the total picture of Friedreich's disease as the long-recognized neurologic changes.

Unfortunately, the cardiac evaluation of both the mother and the father included in this report revealed little which might have been informative relative to the hereditary aspect of the cardiopathy associated with the Friedreich's disease of their 5 children. It is our opinion that the mother has rheumatic heart disease with involvement of the mitral valve. This impression is based on the history of "growing pains" and scarlet fever, on the typical auscultatory findings of mitral valvulitis and on the orthodiascopic evidence of the left auricular dilatation. Her electrocardiogram was essentially normal. In the case of the father, it is our impression that the murmur described is functional. It may be significant, however, that the father's electrocardiogram showed alterations which, though less pronounced, were suggestively similar to the changes seen in the children's tracings.

Undoubtedly, with more widespread recognition of the cardiac abnormalities associated with Friedreich's ataxia, there will result an increased

volume of data encompassing the physical, fluoroscopic and electrocardiographic findings in these cases. A more clearcut and valid understanding should be gained thereby concerning the nature and relationship of the established cardiopathy and the neurologic changes of Friedreich's disease.

SUMMARY

The literature on the cardiac complications of Friedreich's ataxia is reviewed. An analysis is given of the cases of 5 siblings having Friedreich's ataxia, with cardiac findings of remarkable similarity on auscultatory, orthodiascopic and electrocardiographic examination.

The significance of the cardiac abnormalities is discussed in regard to the work and opinions of past investigators and as related to the observations on these 5 siblings.

It is emphasized that additional attention must be directed toward the cardiopathy so frequently associated with Friedreich's ataxia.

Dr. Mabel G. Masten originally referred to us 3 of the members of the family reported on and supplied data relative to the neurologic status of the 5 siblings. Dr. Hans J. Van Baaren and Dr. Erwin H. Ackerknecht assisted in translating the foreign references.

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RECENT PROGRESS IN INSULIN PHYSIOLOGY

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VON MERING and Minkowski [1] in 1889 made the fundamental discovery that total extirpation of the pancreas in dogs produces a disease which resembles ordinary human diabetes mellitus in all important features (glycosuria, hyperglycemia, ketonuria and loss of body weight). Such dogs usually died after two or three weeks in diabetic coma. Minkowski [2] further demonstrated that diabetes did not occur if after pancreatectomy a sizable share of the gland was implanted outside the peritoneal cavity, thus proving the inner secretory nature of the antidiabetic principle of the pancreas. As the histologic origin of the external secretion of the pancreas (i. e., pancreatic juice and its various digestive enzymes) was accounted for by the acinar epithelial cells which secrete into the open ducts, the origin of the internal secretion was logically looked for in accumulations of histologically different epithelial cells which are scattered throughout the pancreas and not connected with any duct. These were first described by Langerhans [3] in 1869 and subsequently called "Langerhans' islets" (LaGuesse, 1893 [4]). The name "insuline" for the as yet hypothetic internal secretion of the islands of Langerhans appeared as early as 1909 (de Meyer [5]). It should be remarked that about the same period the histologists, after earlier observations [6] that more than one type of epithelial cell was present in the islands of Langerhans, succeeded, on the development of special differential stains, in demonstrating at least two different cell types which were called α and β cells. They are distinguished by

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characteristic granulations.[7] In subsequent studies granulated δ cells were described in human material (Bloom, 1931 [8]) and later interpreted as modified (aged) α cells (Gomori, 1941 [9]). Under certain conditions all three cell types mentioned may undergo degranulation. Granulation is regarded as presumptive evidence of secretory function. At present, the staining technic (chromium-hematoxylin-phloxin method) developed by Gomori,[9a] of the University of Chicago, is referred to as most widely applicable in various species and highly suitable for the study and demonstration of α and β cells.

These histologic intricacies were to become important for the explanation of early complications and recent developments in insulin physiology. In 1921 Banting and Best [10] in their ingenious experiment succeeded in extracting insulin from the pancreas of a dog with previously ligated ducts and thus laid the foundation for the subsequent manufacture of insulin from beef and pork pancreas. Principles for the large scale manufacture of insulin were worked out by Collip (isoelectric precipitation near p_H 5.3) and Lilly insulin (iletin®) was the first commercial preparation available in the United States (January to July 1923). From all experimental and pathologic evidence it has been concluded that the β cells of the islands of Langerhans are the producers of insulin and that the β granules are the morphologic expression of insulin content. There have been well reasoned doubts, however, whether the insulin which is obtained by the now traditional methods of extraction and precipitation is really the genuine insulin [11] as stored in the β cell. In fact, insulin precipitated from commercial solutions by histologic fixatives does not show the staining properties of the β granules.[9b] The function of the α cells remained unknown.

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ACTION OF INSULIN

The important effects of insulin in vivo include: (*a*) promotion of the oxidation of glucose by the tissues (the respiratory quotient rises) and corresponding reduction of the blood sugar level, (*b*) deposition of glycogen in liver and musculature, (*c*) regulation (inhibition) of sugar formation from proteins and possibly fat in the liver (gluconeogenesis) and (*d*) promotion of the deposition of fat from dietary glucose and prevention of ketosis. Diagrams explaining the various biochemical reactions in the metabolism of carbohydrate, protein and fat and their complicated interrelations have been drawn up by various researchers in the field [12] but cannot be presented in detail here for lack of space. The search for the specific mechanism of the action of insulin has been relentless. Insulin is a hormone, and apparently hormones do not initiate any new metabolic processes in the body but rather influence the rate of speed of existing processes by accelerating or inhibiting certain enzymatic reactions in the cell on which they act.[13] After previous indications that insulin is involved in the metabolism of organic phosphate compounds, special interest centered in the first step of the utilization of glucose by animal tissue, the phosphorylation of glucose to glucose-6-phosphate by adenosine triphosphate (ATP; a nucleotide). This phosphorylation [14] (equation *A*) which is catalyzed by the enzyme hexokinase is a prerequisite for the subsequent biochemical oxidation of glucose. Its transformation to glycogen also proceeds from equation *A* through two further steps which are catalyzed by the enzymes phosphoglucomutase (equation *B*) and phosphorylase (equation *C*).

In 1945 Price, Cori and Colowick [15] stated that the hexokinase reaction (equation *A*) can be inhibited both in vitro and in vivo by extract of the anterior lobe of the pituitary and that this inhibition

12. Soskin, S., and Levine, R.: Carbohydrate Metabolism, Chicago, University of Chicago Press, 1946. Stetten, D. W., Jr.: Proc. Am. Diabetes A. **7**:69, 1947. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 5, Baltimore, Williams & Wilkins Company, 1950.

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14. The equations for phosphorylation are summarized as follows:

(*A*) Glucose + adenosine triphosphate $\xrightarrow[\text{(hexokinase)}]{}$ glucose-6-phosphate + adenosine diphosphate

(*B*) Glucose-6-phosphate ("Robison ester") $\underset{\text{(phosphoglucomutase)}}{\rightleftarrows}$ glucose-1-phosphate

(*C*) Glucose-1-phosphate ("Cori ester") $\underset{\text{(phosphorylase)}}{\rightleftarrows}$ glycogen + inorganic phosphate

15. Price, W. H.; Cori, C. F., and Colowick, S. P.: J. Biol. Chem. **160**:633, 1945.

is abolished by insulin. This was followed by a report[16] that the hexokinase activity of the muscles and liver from alloxan diabetic rats is decreased. These and subsequent experiments (1947) of the Cori group[17] involving the antagonism between adrenal cortex extract and insulin gave rise to considerable discussion which is still going on.[18]

PARADOXIC REACTIONS; EARLY FRACTIONATION OF INSULIN

As early as 1923 a seemingly paradoxic phenomenon was observed during the investigation of pancreatic extracts and of certain insulin preparations, namely, fractions with blood sugar–raising properties were encountered.[19] In a following report of the same year Kimball and Murlin[20] were of the opinion that a substance different from insulin must be present and mentioned that "This substance has been given the name *glucagon*. . . ." Subsequently, when technical insulin preparations became generally available, numerous authors[21a] described the paradoxic "initial insulin hyperglycemia" lasting fifteen to twenty minutes, which was obtained on intravenous injection but not after subcutaneous administration. This trait was also shown by Lilly insulin.[21b] Murlin did not follow up his theory systematically and, as the early insulin preparations were still comparatively crude, the possibility of various impurities or of an initial physiologic counter-reaction by the adrenal glands had to be considered. Bürger and his associates started investigating this problem in 1928.[22] They established that the hyperglycemic principle of technical insulin preparations (dry samples without preservatives) acted on the liver by mobilization of glycogen and that the adrenal glands did not participate in this effect.

16. Price, W. H.; Slein, M. W.; Colowick, S. P., and Cori, G. T.: Federation Proc. **5**:150, 1946. Cori, C. F.: Enzymatic Reactions in Carbohydrate Metabolism, in Harvey Lectures, 1945-1946, Baltimore, Williams & Wilkins Company, 1947, vol. 41, p. 253.

17. Colowick, S. P.; Cori, G. T., and Slein, M. W.: J. Biol. Chem. **168**:583, 1947.

18. Broh-Kahn, R. H., and Mirsky, I. A.: Science **106**:148, 1947. Christensen, W. R.; Plimpton, C. H., and Ball, E. G.: J. Biol. Chem. **180**:791, 1949. Stadie, W. C., and Haugard, N.: Ibid. **177**:311, 1949.

19. Murlin, J. R.; Clough, H. P.; Gibbs, B. F., and Stokes, H. M.: J. Biol. Chem. **56**:252, 1923. Collip, J. B.: Am. J. Physiol. **63**:391, 1923.

20. Kimball, C. P., and Murlin, J. R.: J. Biol. Chem. **58**:337, 1923.

21. (*a*) Cited by Bürger and Brandt: Ztschr. f. d. ges. exper. med. **96**:375, 1935. (*b*) Collens, W. S., and Murlin, J. R.: Proc. Soc. Exper. Biol. & Med. **26**:485, 1929.

22. Bürger, M., and Kramer, H.: Klin. Wchnschr. **7**:745, 1928; Ztschr. f. d. ges. exper. Med. **61**:449, 1928. Bürger, M.: Verhandl. deutsche Kong. f. inn. Med. **40**:249, 1928; Verhandl. d. deutsch. Gesellsch. f. inn. Med. **41**:508, 1929; Am. J. Physiol. **90**:302, 1929. Bürger, M., and Kramer, H.: Ztschr. f. d. ges. exper. Med. **65**:487, 1929; **67**:441, 1929; **69**:57, 1929. Bürger, M.: Klin. Wchnschr. **9**:104, 1930.

They further showed (1930 to 1933) [23] that specified crystalline insulin preparations were free of the hyperglycemic factor ("Toronto Special," supplied by Dr. C. H. Best; "Abel," supplied by Dr. John J. Abel of Baltimore; "Bonn," prepared in Bürger's laboratory from Squibb insulin according to the method developed by Abel and his associates [23d]). When technical insulin was inactivated by mild alkali, a pure hyperglycemic effect remained. Possible impurities in the nature of other hitherto known substances with hyperglycemic properties were thoroughly considered and either proved to be absent or ruled out as ineffective in the minimal dosage employed. From the appraisal of the extraction procedure used in industry and from his own experiments, which proved the presence of the hyperglycemic principle in fresh pancreatic extract made immediately after the animal (pig) was killed, Bürger concluded that the hyperglycemic component was not a secondary degradation product of the insulin or of other accompanying substances in the extract but that it was an independent physiologic principle preformed in the pancreas itself.

Having noticed that Wellcome insulin hydrochloride was particularly rich in the factor, Bürger and Brandt [24] in 1935 subjected this preparation to a laborious fractionation, during which they eliminated most of the insulin. At p_H 4.38, they obtained a fraction (A_{4a}) which in a dose of 0.02 mg. (20 micrograms) per kilogram of body weight in the fasting rabbit caused a maximal rise in blood sugar of 50 per cent above the starting value and maintained hyperglycemia for an average of forty (maximal sixty) minutes. For practical purposes they called this preparation "glukagon" (in deference to Murlin), although it was not yet entirely free of insulin. In the same year Sopp [25] in Bürger's laboratory, by using a different method of fractionation, obtained glukagon free of insulin. Glukagon was found to be a protein with chemical and physical properties similar to those of insulin, thus rendering its separation and isolation extremely difficult. The only outstanding chemical difference between these two proteins was demonstrated in their reduction values for potassium ferricyanide solution; as computed from titrations, 1 mg. of Wellcome insulin reduced 1.726 mg. of potassium ferricyanide and 1 mg. of glukagon (fraction A_{4a} [24]) reduced 1.287 mg. of potassium ferricyanide. Bürger regarded the glukagon as an endocrine secretion of the pancreas.[26] Recently, after

23. (*a*) Bürger and Kramer.[11a] (*b*) Bürger, M.: Klin. Wchnschr. **10**:351, 1931. (*c*) Bruch, E.: Arch. f. exper. Path. u. Pharmakol. **173**:439, 1933. (*d*) Abel, J. J.; Geiling, E. M. K.; Rouiller, C. A.; Bell, F. K., and Wintersteiner, O.: J. Pharmacol. & Exper. Therap. **31**:65, 1927. (*e*) Du Vigneaud, V.: Jensen, H., and Wintersteiner, O.: Ibid. **32**:367, 1928.

24. Bürger, M., and Brandt, W.: Ztschr. f. d. ges. exper. Med. **96**:375, 1935.

25. Sopp, J. W.: Ztschr. f. d. ges. exper. Med. **96**:817, 1935.

26. Bürger, M.: Klin. Wchnschr. **16**:361, 1937.

obtaining evidence from combined dextrose tolerance and blood transfusion experiments that this principle circulates in the blood and causes hyperglycemia in the receptor,[27] he declared it to be a physiologic hormone of carbohydrate metabolism and a synergist of insulin (1947).[28] Considering that after interruption of circulation through the liver glukagon becomes ineffective while the blood sugar–lowering effect of insulin is not diminished, Bürger concluded that glukagon is not a true anti-insulin and explained the physiologic synergism of the two hormones as follows:

> After a physiologic stimulus due to alimentary sugar, and perhaps also under the impulse of major physical effort, the pancreas first responds by releasing into the blood increased amounts of glukagon which mobilize hepatic glycogen. The increase in blood sugar caused by this mechanism is balanced by a secondary increase of insulin secretion, resulting in an accelerated metabolism of glucose in the tissues, especially in the musculature.

EXPERIMENTAL DIABETES

While the significance of the results obtained at Bürger's laboratory during the period 1930 to 1935 was not yet generally realized, additional evidence came in from other sides, based on the study of two new types of experimental diabetes and their comparison with "surgical" diabetes.

In 1937 Young[29] produced permanent diabetes in dogs through a series of intraperitoneal injections (sixteen to twenty-six days) of the anterior pituitary extract of ox. Since 1938 the experiments have been repeated[30] with three remarkable observations: 1. Permanent diabetes after injection of anterior pituitary extract was different from that produced by extirpation of the pancreas; the animals diabetic as a result of the injection of extract of the anterior lobe of the pituitary (A. P. E. diabetic animals) were able to survive for many months, "apparently indefinitely," without insulin therapy, while depancreatized dogs without insulin will live only two to three weeks at the most. 2. When insulin was given to control glycosuria and ketonuria, the requirement ran much higher (4.4 units per kilogram of body weight or 60 to 75 units daily) than that for the average depancreatized dog (2.5 units per kilogram of body weight[31]). 3. Microscopic examination of sections of pancreas after special differential staining revealed hypertrophy and various degrees of degranulation, degeneration and atrophy of the

27. Bürger, M., and Klotzbücher, E.: Ztschr. f. d. ges. inn. Med. **2**:43, 1947.

28. Bürger, M.: Ztschr. f. d. ges. inn. Med. **2**:311, 1947. Bürger.[26]

29. Young, F. G.: Lancet **2**:372, 1937.

30. Richardson, K. C., and Young, F. G.: Lancet **1**:1098, 1938. Young, F. G.: Brit. M. J. **2**:393, 1939; New England J. Med. **221**:635, 1939. Richardson, K. C.: Proc. Roy. Soc., London, s. B **128**:153, 1940.

31. Dragstedt, L. R.; Allen, J. G., and Smith, E. M.: Proc. Soc. Exper. Biol. & Med. **54**:292, 1943.

β cells, mostly without damage to the α cells. From these investigations and those of other authors on A. P. E. diabetic dogs [32] and cats,[33] it has been concluded [34] that the anterior pituitary extract does not injure the β cells directly but, by interference with physiologic insulin action, produces hyperglycemia (through gluconeogenesis); this puts an overburden on the β cells in the form of an excessive insulin requirement which, if continued long enough, leads to their exhaustion and final degeneration. However, discussion of the biochemical mechanisms involved persists.[35] The study of the histologic changes in the islets produced in both temporary and permanent A. P. E. diabetes and their comparison with those in human diabetes contributed largely to the modern concept that the β cells can undergo both functional and anatomic changes, that in human diabetes there is a continuous struggle between degenerative changes and regenerative activity and that the pancreas is not a static organ (like the brain or myocardium) but is, within certain limits, able to repair itself after injury.[36] This is supported by clinical experience: "It is evident that every diabetic patient who has been given a regulated dietary regimen with corresponding physical exercise experiences an increase of carbohydrate tolerance. This we know for certain from the preinsulin era." [37]

The quickest way of producing permanent experimental diabetes chemically was pointed out in 1943 when Dunn and his co-workers [38] (in Glasgow, Scotland) injected alloxan into rabbits intravenously.[39] After an initial rise in blood sugar, the animals died in hypoglycemic shock and autopsy revealed acute necrosis (undifferentiated) of the islands of Langerhans. Subsequently, the Glasgow investigators [40] and

32. (*a*) Best, C. H.; Campbell, J. H., and Haist, R. E.: J. Physiol. **97**:200, 1939. (*b*) Haist, R. E.; Campbell, J., and Best, C. H.: New England J. Med. **223**:607, 1940. (*c*) Ham, A. W., and Haist, R. E.: Am. J. Path. **17**:787, 1941.

33. (*a*) Lukens, F. D. W., and Dohan, F. C.: Endocrinology **30**:175, 1942. (*b*) Lukens, F. D. W.; Dohan, F. C., and Wolcott, M.: Ibid. **32**:475, 1943.

34. (*a*) Gomori.[9b] (*b*) Goldner, M. G., and Gomori, G.: Proc. Am. Diabetes A. **4**:89, 1944.

35. Conn, J. W.; Louis, L. H., and Wheeler, C. E.: J. Lab. & Clin. Med. **33**:651, 1948. Conn, J. W.; Louis, L. H., and Johnston, M. H.: Ibid. **34**:255, 1949.

36. Gomori.[9b] Ham and Haist.[32c] Footnote 33. Warren, S., and Root, H. F.: Am. J. Path. **1**:415, 1925. Warren, S.: The Pathology of Diabetes Mellitus, ed. 2, Philadelphia, Lea & Febiger, 1938.

37. Bürger, M.: Med. Klin. **36**:1270, 1940.

38. Dunn, J. S.; Sheehan, H. L., and McLetchie, N. G. B.: Lancet **1**:484, 1943.

39. Alloxan was first prepared by Friedrich Wöhler (*Ann. d. Pharm.* **24**:241, 1838) by oxidation of uric acid. This is the same chemist who had become famous in 1828 by his laboratory synthesis of urea, signifying the end of the "vitalistic doctrine" in organic chemistry.

40. Dunn, J. S., and McLetchie, N. G. B.: Lancet **2**:384, 1943.

others [41] working with various species were able to adjust the dosage to tide their animals over the secondary hypoglycemia. They reported as a final result severe permanent diabetes twenty-four to forty-eight hours after injection. Goldner and Gomori (1944)[41b] described the lesions as selective degranulation and necrosis of the β cells, the α cells being intact or even proliferating, as shown by their differential staining technic. The β cells were damaged within the first few minutes after alloxan injection. Of particular interest was the work carried on in dogs [42]; it was noticed that the hyperglycemia of the alloxan diabetic dogs appeared sometimes to be severer than that usually seen in depancreatized dogs and that without insulin therapy some of the alloxan diabetic dogs lived about twice as long (six to seven weeks) as depancreatized animals (two to three weeks). Alloxan diabetes can be prevented, i. e., the β cells can be protected against the toxic effect of alloxan by large doses of cysteine or glutathione, which are biologically important sulfur-containing amino acids, given intravenously immediately (one to two minutes) preceding the alloxan injection (experiments with rats of Lazarow [43]). This discovery stimulated many interesting experiments and theories about the mechanism of alloxan toxicity in the β cell, the final explanation of which is still lacking.[44]

In 1945 Thorogood and Zimmermann [45] (Harvard University) reviewed the situation and proceeded with a series of ingenious and logical experiments. Dogs were made severely diabetic with alloxan (i. e., their β cells were destroyed); their insulin requirement averaged 3.5 units per kilogram of body weight. Fourteen to thirty-one days afterward the pancreas was removed (which means the dogs were also deprived of their α cells); the insulin requirement dropped to an average of 1.2 unit per kilogram of body weight, i. e., to almost one third. The insulin requirement of 4 alloxan diabetic dogs was as follows:

Before Pancreatectomy, Units	After Pancreatectomy, Units
34	12
76	30
60	20
36	12

41. (*a*) Bailey, C. C., and Bailey, O. T.: Production of Diabetes Mellitus in Rabbits with Alloxan: Preliminary Report, J. A. M. A. **122**:1165 (Aug. 21) 1943. (*b*) Goldner, M. G., and Gomori, G.: Endocrinology **33**:297, 1943. (*c*) Lukens, F. D. W.: Physiol. Rev. **28**:304, 1948.

42. Footnotes 34b and 41b.

43. Lazarow, A.: Anat. Rec. **91**:24, 1945; Proc. Soc. Exper. Biol. & Med. **61**:441, 1946.

44. Lazarow, A.: Physiol. Rev. **29**:61, 1949.

45. Thorogood, E., and Zimmermann, B.: Endocrinology **37**:191, 1945.

It was noticed that the alloxan diabetic dogs secreted less ketone bodies in their urine than the pancreatectomized (von Mering and Minkowski [1]) dogs, and it was observed again that untreated alloxan diabetic dogs, although their glycosuria was higher, lived much longer than untreated pancreatectomized dogs. Thorogood and Zimmermann stated that ligation of the pancreatic ducts and the attendant degeneration of the exocrine acinar tissue did not materially affect the course of alloxan diabetes and concluded that an endocrine pancreatic factor was responsible for the observed differences between these two types of diabetes. In order to arrive at a satisfactory explanation for the difference between the physiologic picture of pure β cell deficiency (alloxan diabetes) and that which characterizes complete removal of the pancreas (the diabetes of von Mering and Minkowski), they postulated the existence of a second pancreatic hormone which causes hyperglycemia and inhibits formation of ketone bodies in the insulin-deficient animal. This was most likely an α cell hormone of the islands of Langerhans. Independently, Rodriguez-Candela [46] (Spain) had arrived at similar results.

This fine work of Thorogood and Zimmermann has thrown light on seemingly paradoxic observations in clinical surgery. Patients who underwent complete pancreatectomy were observed to have an unexpectedly low insulin requirement, much less than that of many spontaneously diabetic patients.[47] "The remarkable thing about these patients is that with no pancreas at all, none of them has required more than 40 units of insulin a day." [48] This showed that in spontaneous diabetes more than a simple insulin deficiency is involved. Pointing in the same direction are previous experiences gained by Dragstedt and his co-workers [81] from surgery of the pancreas in dogs. When dogs became diabetic after a partial (subtotal) pancreatectomy ("Sandmeyer diabetes" due to exhaustion of remaining β cells), their insulin requirement was far greater (about two and a half times) than that of a control series which had undergone a complete pancreatectomy.

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46. Rodriguez-Candela, J. L.: An. Acad. méd.-quir. españ., 1945-1946, vol. 29; cited in Anti-Insulinic Substances of Pancreatic Origin, Foreign Letters (Madrid), J. A. M. A. **134**:1503 (Aug. 23) 1947; Rev. clín. españ. **19**:326, 1945, cited by Lukens,[41e] p. 310.

47. Goldner, M. G., and Clark, D. E.: J. Clin. Endocrinol. **4**:194, 1944. Brunschwig, A.; Ricketts, H. T., and Bigelow, R. G.: Surg., Gynec. & Obst. **80**:252, 1945. Dixon, C. F.; Comfort, M. W.; Lichtman, A. L., and Benson, R. E.: Total Pancreatectomy for Carcinoma of the Pancreas in a Diabetic Person: Metabolic Studies, Arch. Surg. **52**:619 (June) 1946. Waugh, J. M.; Dixon, C. F.; Clagett, O. T.; Bollman, J. L.; Sprague, R. G., and Comfort, M. W.: Proc. Staff Meet., Mayo Clin. **21**:25, 1946. Ricketts, H. T.; Brunschwig, A., and Knowlton, K.: Am. J. Med. **1**:229, 1946.

48. Ricketts, H. T.: Cleveland Clin. Quart. **16**:112, 1949.

RECENT FRACTIONATION OF INSULIN

In recent years, the interest in the biochemical fractionation of technical insulin was revived. In January 1947 two Belgian physiologists, Bouckaert and de Duve [49] (Louvain University), criticized Lilly insulin as being contaminated by a hyperglycemic factor which they stated was not contained in a Danish preparation (Novo insulin). In November 1947, de Duve and Hers [50] mentioned it again and commented bitterly: "The use of such contaminated insulins for experimental purposes can give rise to grave errors. Their therapeutic application, however, appears rarely contraindicated." They emphasized the "very fleeting action" as a characteristic feature of the hyperglycemic factor and pointed out that for the evaluation of its importance the "contaminated" insulin preparation must be administered by continuous intravenous injection and its action compared with the effect of a pure insulin preparation under the same conditions. In February 1948 appeared a communication from Heard and his associates [51] (McGill University, Montreal, Canada), who had checked various pancreatic fractions in the course of separation of crystalline zinc insulin; their starting materials came from the Connaught Laboratories, in Toronto. They concentrated a pancreatic extract which remained after the first isoelectric precipitation of insulin and inactivated the rest of the insulin in their concentrate. When injected into rats (intraperitoneally), such an extract always caused a drop in the glycogen content of the liver (e. g., from 3.78 to 1.22 per cent) and a considerable rise in blood sugar (e. g., from 106 to 193 mg. per hundred cubic centimeters). When tested against rat liver slices directly, there was an increase of 20 to 30 per cent in glucose production. This report received widespread attention because the Montreal workers, after summing up the previous evidence, for the first time assigned the name "α cell hormone" to the hyperglycemic principle associated with technical insulin. Aside from this the hormone was not actually isolated and the preparation was apparently still highly crude when the high dose employed by the Montreal group (14 mg. of nitrogen equaling approximately 88 mg. protein; after purification, 2 mg. of nitrogen equaling approximately 12.5 mg. of protein per rat) is compared with the more than a thousand times smaller dose in which Bürger's material was effective.

Independently, extensive investigations on the same problem had been started by Sutherland and his collaborators [52] in Cori's laboratory

49. Bouckaert, J. P., and de Duve, C.: Physiol. Rev. **27**:38, 1947.

50. de Duve, C., and Hers, H. G.: Compt. rend. Soc. de biol. **141**:1147, 1947.

51. Heard, R. D. H.; Lozinski, E.; Stewart, L., and Stewart, R. D.: J. Biol. Chem. **172**:857, 1948.

52. (*a*) Sutherland, E. W., and Cori, C. F.: J. Biol. Chem. **172**:737, 1948. (*b*) Sutherland, E. W., and de Duve, C.: Ibid. **175**:663, 1948. (*c*) Sutherland, E. W.; Cori, C. F.; Haynes, R., and Olsen, N. S.: Ibid. **180**: 825, 1949.

in St. Louis; their publications appeared between February 1948 and September 1949. The presence of the hyperglycemic-glycogenolytic (H-G) factor (as they called it) in both crystalline and amorphous Lilly insulin was confirmed just as was its absence from the Danish crystalline Novo insulin. The hyperglycemic-glycogenolytic factor is apparently a protein acting on the phosphorylase enzyme system in the hepatic cells, i. e., the conversion of glycogen to glucose-1-phosphate (cf. equation C^{14}). It is not formed from insulin itself in the course of the usual procedure of extraction and isolation. Ordinarily, the hyperglycemic-glycogenolytic factor follows the insulin through the various steps of its purification but it can be completely removed by adequate methods of crystallization (done by Novo Terapeutisk Laboratorium, later also by Eli Lilly & Co.). The greatly increased yield of the H-G factor per weight unit from fetal calf pancreas and from pancreas sclerosed after duct ligation was strong evidence for its production by the islet cells. When rabbits were made diabetic with alloxan (which destroys the β cells), extracts prepared from their pancreases had a pure and prolonged hyperglycemic action, unopposed by insulin. (No attempt was made to prepare the pure factor from such a source). This narrowed it further down to the α cells as the producers of the factor. A most interesting fact emerged when Sutherland and de Duve [52b] were also able to extract the hyperglycemic-glycogenolytic factor (without insulin effect) from the upper two thirds of the gastric mucosa of the dog; this mucosa was found to be half as active as pancreatic tissue. (Extract of rabbit stomach also contained the factor, but similar extracts from hog, beef and sheep did not.) It was noted that the factor when added to blood was destroyed at an appreciable rate. The hyperglycemic-glycogenolytic factor could not be demonstrated in other tissues. As an explanation, the St. Louis group cited histologic evidence that certain argentophilic cells are particularly numerous in the fundus of the gastric mucosa of the dog [53] and that, besides, argentophilic cells in the pancreas have been identified by some authors [54] as the α cells. They expressed the view that the H-G factors of the gastric mucosa of the dog and of the pancreas are "closely related or identical" and that the H-G factor "may originate in the α cells." They did succeed in actually isolating from amorphous and crystalline Lilly insulin fractions of hyperglycemic-glycogenolytic factor (as dry substance) with pure hyperglycemic activity, the potency of which was about ten times as high as that of the starting material. While the glycogenolytic effect on liver slices was demonstrated with an amount as small as 0.7 micrograms, they used 0.45 mg. (450 micrograms) as an intravenous dose in the rabbit, which is approxi-

53. Tehver, H.: Ztschr. f. mikr.-anat. Forschr. **21**:462, 1930.

54. (*a*) van Campenhout, E.: Proc. Soc. Exper. Biol. & Med. **30**:617, 1933. (*b*) Ferner, H.: Ztschr. f. mikr.-anat. Forsch. **44**:451, 1938.

mately 225 micrograms per kilogram of body weight. There was a prolonged hyperglycemic effect lasting forty to sixty minutes, with a maximum rise of 50 mg. per hundred cubic centimeters above the starting value (90 mg.). As the minimum dose to demonstrate this effect, unfortunately, was not determined, Bürger can still claim that his glukagon was about five to ten times stronger in the rabbit test. Purification of the hyperglycemic-glycogenolytic factor from gastric mucosa (St. Louis group) resulted in preparations effective at 12 micrograms in the liver slice test and at 1 mg. (approximately 500 micrograms per kilogram of body weight) in the rabbit test. When amorphous and crystalline Lilly insulin were subjected to electrophoresis and the resulting patterns analyzed, a separate compound was observed to migrate at a slightly slower rate than insulin and quite close to it. The comparative amount of this compound was about 10 per cent. As it was absent from electrophoretic patterns of Novo insulin, it was presumed to represent the proportion of the hyperglycemic-glycogenolytic factor. From this the St. Louis group concluded that commercial insulin preparations contain up to 10 per cent of the hyperglycemic factor.

In the meantime Eli Lilly & Company have proceeded to manufacture an insulin free of this factor which is available on special request.

In summary, it becomes evident that the action of the hyperglycemic principle is fleeting when administered intravenously in conjunction with insulin, which opposes its effect, but that the effect is prolonged when insulin action is eliminated. As a separate compound it has not yet been prepared in stable form except in minute amounts; its solutions undergo gradual loss of potency. On subcutaneous administration it is ineffective, presumably because of its rapid destruction by blood and tissue fluids. Hyperglycemia is effected by glukagon in dilute concentrations of the same range as apply to insulin for the production of hypoglycemia. An interesting communication was received recently stating that Ferner also had indicated at an earlier period that glukagon is produced by the α cells (1938 to 1942).[55] The present status of glukagon reminds one of that of insulin during the era before Banting and Best when the existence of the hormone was evident but its isolation and preparation were beset with difficulties.

FATE OF INSULIN IN THE BODY

Physiologists and clinicians have speculated about the ultimate fate of insulin in the body. Insulin administered subcutaneously disappears from the body within eight hours and within considerably less time

55. Bürger, M.: Personal communication to the author on Ferner.[54b] Ferner, H.: Anat. Anz. **88** (supp.): 104, 1939; Virchows Arch. f. path. Anat. **309**: 87, 1942.

after intravenous injection. Mirsky and his associates,[56] after stating that previous investigations by other authors on the urinary excretion of insulin had led to conflicting reports, determined in 1948 that normal human subjects secreted only 0.16 ± 0.04 unit of insulin in the urine per day, which is negligible. Mildly diabetic patients (not needing insulin) secreted only 0.07 ± 0.03 unit. From a patient receiving 400 units of insulin intravenously during shock therapy only 0.59 unit was recovered within twenty-four hours; this amounted to only 0.1 per cent of the injected insulin (after deduction of 0.16 unit derived from endogenous insulin). It was generally assumed that both endogenous and exogenous insulin are rapidly destroyed in the organism, but knowledge of the site and mechanism of this destruction was incomplete. Mirsky and Broh-Kahn [57] cited Schmidt and Saatchian,[58] besides Lehmann and Schlossmann,[59] as having obtained evidence that animal tissues can inactivate insulin in vitro. Mauriac and Aubertin [60] observed that normal blood, plasma or cells inhibit insulin action; they also reported that diabetic blood inhibits insulin action more than does normal blood. Karelitz and his associates,[61] who used commercial insulin solutions (1930), reported that blood cells in vitro caused a greater (two times) inactivation than plasma. This effect was multiplied (two and a half to three times) when the blood cells were laked; it was concluded from this that the inactivating factor of the blood is mainly intracellular. Even greater inactivation was caused by blood from patients with diabetes, myeloid leukemia, purulent infections (empyema), artificially produced fever (bacterial vaccine) and serum sickness and by pus. The authors emphasized that enough plasma or blood be taken to obtain demonstrable in vitro inactivation or inhibition of 3 units of insulin within one to two hours (the maximum normal plasma requirement was 15 cc., with correspondingly less for blood cells, laked blood cells, etc.). Defined incubation mixtures were injected into rabbits subcutaneously and the blood sugar curves followed for three hours. Karelitz and his

56. Mirsky, I. A.; Podore, C. J.; Wachman, J., and Broh-Kahn, R. H.: J. Clin. Investigation **27**:515, 1948.

57. (*a*) Mirsky, I. A., and Broh-Kahn, R. H.: Arch. Biochem. **20**:1, 1949. (*b*) Broh-Kahn, R. H., and Mirsky, I. A.: Ibid. **20**:10, 1949. (*c*) Simkin, B.; Broh-Kahn, R. H., and Mirsky, I. A.: Ibid. **24**:422, 1949.

58. Schmidt, A. A., and Saatchian, R. L.: Zhur. exper. biol. i med. (Moscow) **11**:42, 1929.

59. Lehmann, H., and Schlossmann, H.: J. Physiol. **94**:15, 1938.

60. Mauriac, P., and Aubertin, E.: Compt. rend. Soc. de biol. **98**:233, 235 and 237, 1928; cited by Karelitz, S.; Cohen, P., and Leader, S. D.: Arch. Int. Med. **45**:546 (April) 1930.

61. Karelitz, S.; Cohen, P., and Leader, S. D.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro: Effect of Normal and of Diabetic Blood on Insulin Action, Arch. Int. Med. **45**:546 (April) 1930. Karelitz, S.; Leader, S. D., and Cohen, P.: Insulin Inactivation by Human Blood Cells and Plasma in Vitro: Effect of Insulin, ibid. **45**:690 (May) 1930.

associates showed that the insulin-destroying principle of plasma, whole blood cells and pus is thermolabile and becomes inactivated by heat of 55 to 60 C.(131 to 140 F.); at ice box temperatures the insulin-destroying principle is inhibited. From their observations, which also included a study of the p_H range, Karelitz and his co-workers concluded that the insulin-destroying principle is most likely "an enzyme or an enzyme-like substance." In their opinion its relative physiologic and pathologic importance could not yet be fully evaluated. Bürger and his associates [62] who used crystalline insulin (0.04 mg. to 4 cc. of blood, etc.[28]) for their in vitro experiments, arrived at results which were similar to those of Karelitz but differed through the proportionally much longer periods which were needed to obtain insulin inactivation. They further made the interesting observation that in normal persons the inactivation of insulin through blood proceeds more rapidly with advancing age. Average inactivation times were (*a*) in healthy persons under 20 years of age, twenty-eight to thirty-two hours; in persons 20 to 60 years of age, twenty-three to twenty-six hours; in persons over 60, twenty to twenty-two hours; (*b*) in diabetic persons, 9 hours, and (*c*) in leukemic persons (with a white blood cell count of greater than 100,000), two to three hours. From laboratory and clinical experience Bürger concluded that leukocytic enzymes and other as yet unknown insulin-destroying principles in both blood and tissues were responsible. Inactivation of insulin in vitro on digestion with blood serum or laked red blood cells was also reported by Black.[63]

TISSUES WITH INSULIN-DESTROYING ACTIVITY

Several authors [64] had pointed out that if one judged the effect of insulin from the change in the blood sugar intraportal injection of the hormone was less effective than injection into a peripheral vein. Several attempts to prove inactivation of insulin by the liver from experiments providing for circulatory circumvention of the liver [65] or by direct injection of insulin into the liver or spleen [66] led to conflicting reports. In 1942 Reiner and his associates [67] injected insulin labeled

62. Bürger, M.; Footnotes 26, 28 and 37, Bürger, M., and Kohl, H.: Arch. f. exper. Path. u. Pharmakol. **174**:130, 1934; **178**:269, 1935. Bürger, M.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **49**:23, 1937. Tochtermann: Inaug. Dissert., Bonn, 1938; cited by Bürger,[28] p. 314. Kohl, H.; Selbach, H., and Janning, A.: Arch. f. exper. Path. u. Pharmakol. **185**:212, 1937. Kohl, H.: Ibid. **194**:452, 1940; Klin. Wchnschr. **19**:181, 1940.

63. Black, P. T.: Brit. J. Exper. Path. **14**:318, 1933.

64. Collens and Murlin,[21b] Neuwirth, I.; Co Tui, F., and Wallace, G. B.: Proc. Soc. Exper. Biol. & Med. **27**:194, 1929.

65. Kepinov, L., and Ledebt-Petit-Dutaillis, S.: Compt. rend. Soc. de biol. **97**:25, 1927. Goadby, H. K., and Richardson, J. L.: J. Physiol. **97**:417, 1940.

66. Mark, J., and Lewis, R. C., Jr.: Bull. Johns Hopkins Hosp. **72**:246, 1943.

67. Reiner, L.; Keston, A. S., and Green, M.: Science **96**:362, 1942.

with radioactive iodine into rats (intravenously and intracardially) and studied its absorption and distribution. Relatively large quantities of radioactive material were detected in the liver and kidneys, which suggested concentration of insulin by these organs. In 1947 de Duve [68] studied the glucose requirements for maintenance of dogs after surgical removal of the liver (hepatectomy) and compared them with the amounts needed when additionally the pancreas, or the pancreas plus the remaining viscera is taken. He came to the conclusion that hepatectomy has the effect of exposing the rest of the body to a continuous and massive overdose of insulin, with subsequent death in hypoglycemic shock (and azotemia). Then he continued:

> This does not mean that there is a change in the insulin secretion of the pancreas. One could quite as well admit that in the intact animal the liver intercepts a good portion of the insulin which is secreted by the pancreas and passes through the liver before it reaches the peripheral tissues.

This was a most elegant deduction and, from the figures, practically identical with stating that continuously about one third of the physiologically secreted insulin is inactivated by the liver. In 1949, Mirsky and Broh-Kahn [57] reported that certain tissue extracts from various animals and man were found to destroy the physiologic activity of insulin quite rapidly in vitro.[69] Systems capable of this inactivation of insulin were found to be widely distributed. Rat liver extract showed the greatest activity; extracts from kidney and muscle were progressively less potent, brain extract, whole blood and blood cells even less and plasma the least. The following tabulation was taken from their table 1 [57a]:

Rat Tissue		Pooled Percentages of Initial (Fasting) Blood Sugar
Liver		211
Kidney		150
Muscle		112
Brain		84
Whole blood		92
Blood cells (washed or hydrolyzed)		91
Plasma		55
According to their figure 1 [57a]	Blank test: Saline solution (curve A)	67
	Heat-inactivated liver extract (curve B)	60

68. de Duve, C.: Compt. rend. Soc. de biol. **141**:1145, 1947.

69. One cubic centimeter containing 8 units of purified amorphous Lilly insulin and 1 cc. of rat tissue extract (3 volumes of water were used to 1 volume of tissue) were incubated for one hour. Blood or blood constituents were used undiluted. Rabbits were given an intravenous injection of 1 cc. of the incubation mixture, representing 4 units of insulin prior to incubation. Blood sugar levels, determined thirty and sixty minutes after injection, were calculated as percentage values of the initial (fasting) blood sugar. The sum of the percentages of the thirty and sixty minute blood samples was tabulated as "pooled percentage of initial blood sugar."

The equivalent for complete inactivity would appear in this tabulation at 67 to 60 or below, as determined from blank tests. It is evident from the results that the greatest insulin-destroying action is to be found in liver, kidney and musculature. While Mirsky and Broh-Kahn called the activity of brain extract, whole blood and blood cells of the rat "not appreciable," this conclusion is not quite justified in view of their figures. In an editorial in *The Journal of the American Medical Association* [70] the term "not appreciable" unfortunately was taken to mean "none." These terms, if transferred to human blood, would be contradicted by the experiences of several other authors mentioned previously.[71] Mirsky and Broh-Kahn mentioned that liver from rabbit, steer, chicken and man was also found to be rich in the insulin-destroying principle. They expressed the opinion that this principle is a specific enzyme, for which they suggest the name insulinase. Weisberg and his associates [72] in 1949 tested the effectiveness of equal amounts of insulin injected continuously for two hours via the femoral vein or the splenic vein in normal and depancreatized dogs. The femoral route resulted in a significantly greater depression in blood sugar than the splenic (portal) route. (This was also seen when an insulin preparation was used which was free of the hyperglycemic factor.) In view of the other recent evidence, Weisberg and his associates concluded that a considerable portion of insulin is removed or inactivated as it passes through the liver, presumably by the "insulinase system." They estimated that the liver of the intact dog can inactivate 0.02 to 0.04 unit of insulin per kilogram of body weight per hour; in a dog of 15 Kg. this would amount to 7.2 to 14.4 units of insulin per day.

Although the insulin-destroying activity of the blood has been overshadowed by the newer knowledge of the role which is played by the tissues, especially the liver, the former must not be overlooked, as it was shown that this action of the blood increases considerably with age and specified pathologic conditions. It may be expected that a careful reinvestigation and comparison of the methods used by different investigators will bring about a clarification and reconciliation of the present discrepancies. The discovery and study of one or several insulin-destroying principles will contribute to the realization that various factors are involved in the pathogenesis and clinical picture of diabetes mellitus. A temporary increase in insulin requirements in clinical diabetes, such as occurs during acute infections or some types of prolonged insulin resistance, may well be caused by an accelerated rate of insulin destruction in the body.

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70. Fate of Insulin in the Normal and Diabetic Organism, editorial, J. A. M. A. **140**:1344 (Aug. 27) 1949.

71. Footnotes 60, 61, 62 and 63.

72. Weisberg, H. F.; Friedman, A., and Levine, R.: Am. J. Physiol. **158**:332, 1949.

Progress in Internal Medicine

GASTROENTEROLOGY

A Partial Review of the Literature from July 1948 to July 1949

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From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago School of Medicine.

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INTRODUCTION

THE REVIEW of gastroenterology this year is limited to papers of research significance, clinical and laboratory. Consequently, it has been necessary to omit reference to the splendid books published during the year, important general articles, historical papers, case reports and other valuable contributions. The wide interest in gastroenterologic problems is perhaps reflected in the fact that more than 1,500 articles were read during the preparation of this review.

ESOPHAGUS

Flexible Esophagoscope.—Schindler,[1] Boros[2] and Hufford[3] have each described flexible esophagoscopes.

Nervous Control of Cervical Portion of Esophagus.—The main motor innervation of the cervical portion of the esophagus in the cat and dog is the pharyngoesophageal branch of the vagus nerve. Bilateral section of the vagus trunk in the cat and the dog resulted in paralysis of the esophagus except for the cervical portion. Section of the pharyngoesophageal nerve alone led to temporary paralysis of the entire cervical part of the esophagus and dysphagia, but recovery was complete in three to five weeks.[4]

Esophageal Atresia With and Without Tracheoesophageal Fistula.—Congenital atresia of the esophagus is considered by numerous authors.[5]

1. Schindler, R.: A Safe Diagnostic Optical Esophagoscope, J. A. M. A. **138**:885 (Nov. 20) 1948; Construction and Use of a Safe Diagnostic Optical Esophagoscope, Gastroenterology **12**:355, 1949.

2. Boros, E.: Flexible Tube Esophagoscopy, Gastroenterology **11**:879, 1948.

3. Hufford, A. R.: Flexi-Rigid, Optical Esophagoscope, Gastroenterology **12**:779, 1949.

4. Hwang, K.; Grossman, M. I., and Ivy, A. C.: Nervous Control of the Cervical Portion of the Esophagus, Am. J. Physiol. **154**:343, 1948.

5. Byron, F. X.: Congenital Atresia of the Esophagus with Hypoplasia or Agenesis of the Lower Segment, Surgery **24**:841, 1948. Lisa, J. R., and Taylor, H. M.: Congenital Malformation of the Esophagus Without Tracheo-Esophageal Fistula, New York State J. Med. **48**:1622, 1948. Haight, C.: Congenital Tracheoesophageal Fistula Without Esophageal Atresia, J. Thoracic Surg. **17**:600, 1948. Sandblom, P.: The Treatment of Congenital Atresia of the Esophagus from a Technical Point of View, Acta chir. Scandinav. **97**:25, 1948. Ingalls, T. H., and Prindle, R. A.: Esophageal Atresia with Tracheoesophageal Fistula: Epidemiologic and Teratologic Implications, New England J. Med. **240**:987, 1949. White, R. J.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula, Texas State J. Med. **45**:301, 1949. Bigger, I. A.: The Treatment of Congenital Atresia of the Esophagus with Tracheo-Esophageal Fistula, Ann. Surg. **129**:572, 1949. Ashe, W. M., and Seybold, W. D.: Congenital Atresia of the Esophagus with Tracheoesophageal Fistula Treated by Primary Esophageal Anastomosis: Report of 8 Cases, Proc. Staff Meet., Mayo Clin. **24**:327, 1949. Lam, C. R.: Completing the Multiple-Stage Operation for Atresia of the Esophagus, J. Thoracic Surg. **18**:327, 1949.

Diverticula.—Diverticula of the thoracic portion of the esophagus are discussed by Adams [6] and Harrington.[7]

Heartburn.—This symptom is not dependent on gastric acidity and probably is produced by alterations in tonus of the lower part of the esophagus.[8] Treatment should include discussion with the patient of the nature of the heartburn, instruction in proper eating habits and psychotherapy. According to Kardon,[9] Bartlakowski found that 70 per cent of esophagi contained islands of acid-secreting gastric mucosa in the distal segment. It is suggested that these gastric glands secrete sufficient acid and pepsin locally to supplement that derived from the reflux of gastric juice. Anion exchange resins administered orally rapidly relieved the heartburn accompanying pregnancy in 88 per cent of cases.

Stricture.—Regurgitation of acid gastric secretion probably plays an important role in the causation of esophagitis and benign stricture; a hiatus hernia, duodenal ulcer or esophageal ulcer frequently is present concomitantly. Bougienage and dietary treatment yielded satisfactory results in more than two thirds of 60 cases; when surgical intervention is necessary, the usual operation of choice is resection.[10] Wangensteen and Leven [11] likewise present clinical evidence in support of the thesis that esophagitis and esophageal stricture are consequences of the regurgitation of acid and pepsin into the lower portions of the esophagus; 6 patients were subjected to gastric resection with uniformly successful results. Among 36 patients with stenosis of the esophagus, 20 had bronchopulmonary complications, most frequently bronchiectasis and pneumonitis.[12] In the treatment of lye burns of the esophagus, during the acute stage the patient is given a mouth wash of weak acetic acid, followed by a mouth wash and swallow of a mild bland oil.[13] The stomach is thoroughly washed with dilute acetic acid and water, and a bland oil is instilled. Esophagoscopy is performed on the fourth day to determine

6. Adams, H. D.: Diverticula of the Thoracic Esophagus, J. Thoracic Surg. **17**:639, 1948.

7. Harrington, S. W.: The Surgical Treatment of Pulsion Diverticula of the Thoracic Esophagus, Ann. Surg. **129**:606, 1949.

8. Tumen, H. J., and Cohn, E. M.: Heartburn: A Clinical Study, J. A. M. A. **139**:292 (Jan. 29) 1949.

9. Kardon, S. C.: Anion Exchange Resins in the Treatment of Heartburn During Pregnancy, New England J. Med. **239**:575, 1948.

10. Benedict, E. B., and Sweet, R. H.: Benign Stricture of the Esophagus, Gastroenterology **11**:618, 1948.

11. Wangensteen, O. H., and Leven, N. L.: Gastric Resection for Esophagitis and Stricture of Acid-Peptic Origin, Surg., Gynec. & Obst. **88**:560, 1949.

12. Villalobos, L. M. E.: Las estenosis esofagicas y sus complicaciones broncopulmonares, Rev. de gastro-enterol. de México **14**:65, 1949.

13. Fisher, G. E., and Hicks, J. J.: The Management of Lye Burns of the Esophagus, South. M. J. **41**:591, 1948.

the extent of mucosal damage. Subsequently, the esophagus is dilated daily. Three patients with corrosive strictures of the esophagus were treated successfully by repeated dilation with bougies passed over a previously swallowed string.[14] In patients with multiple strictures and in those with thick fibrous scars in which there is little or no improvement in the course of six to nine months of dilation, gastroesophageal anastomosis is useful.[15] In 2 patients complete strictures of the cervical part of the esophagus due to lye burns were treated successfully by transthoracic substitution of a loop of jejunum for the esophagus.[16]

Spontaneous Rupture.—Spontaneous perforation of the lower portion of the esophagus into the mediastinum or pleural cavity should be considered in the differential diagnosis for any patient with severe upper abdominal pain associated with vomiting, particularly of blood.[17]

Instrumental Perforation.—The importance of prompt surgical intervention is again emphasized.[18]

Varices.—The problem of bleeding esophageal varices is illuminated by several reports.[19]

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14. Lynch, M. G.: Corrosive Strictures of the Esophagus and Their Treatment, South. M. J. **42**:635, 1949.

15. Lynch, M. G.: Strictures of the Esophagus, South. Surgeon **14**:502, 1948.

16. Harrison, A. W.: Transthoracic Small Bowel Substitution in High Stricture of the Esophagus, J. Thoracic Surg. **18**:316, 1949.

17. Kinsella, T. J.; Morse, R. W., and Hertzog, A. J.: Spontaneous Rupture of the Esophagus, J. Thoracic Surg. **17**:613, 1948. Moore, J. A., and Murphy, J. D.: Spontaneous Rupture of the Esophagus, ibid. **17**:632, 1948. Higginson, J. F., and Clagett, O. T.: Complete Disruption of the Esophagus, ibid. **17**:846, 1948. Beal, J. M.: Spontaneous Rupture of the Esophagus, Ann. Surg. **129**:512, 1949. Scholefield, J.: Spontaneous Perforation of the Esophagus, Brit. M. J. **1**:348, 1949. Fincher, E. F., and Swanson, H. S.: Esophageal Rupture Complicating Craniotomy—Symptom Complex and Proposed Surgical Treatment, Ann. Surg. **129**:619, 1949.

18. Bisgard, J. D., and Kerr, H. H.: Surgical Management of Instrumental Perforation of the Esophagus, Arch. Surg. **58**:739 (June) 1949. Wells, C. A.; Hughes, J. H.; Edwards, R., and Marcus, R.: Perforations Following Dilatation of Oesophageal Strictures: A Report of 3 Cases with Recovery, Thorax **4**:119, 1949. Jemerin, E. E.: Results of Treatment of Perforation of the Esophagus, Ann. Surg. **128**:971, 1948. Temple, L. J.: Treatment of Perforations of the Esophagus, Brit. M. J. **1**:935, 1949.

19. Jorup, S.: Congenital Varices of the Esophagus, Acta pædiat. **35**:247, 1948. Davis, H. H.: Esophageal Varices: 2 Cases with Different Surgical Approach, Arch. Surg. **57**:391 (Sept.) 1948. Van Eeckhoutte, P., and Kolff, W. J.: Treatment of Bleeding Esophageal Varices by Tamponade with a Rubber Balloon, Nederl. tijdschr. v. geneesk. **4**:3853, 1948. Weinberg, T.: Observations on the Occurrence of Varices of the Esophagus in Routine Autopsy Material, Am. J. Clin. Path. **19**:554, 1949. Tolan, J. F.: Esophageal Varices and Their Treatment by Injection, Laryngoscope **59**:425, 1949.

Cardiospasm.—Acetyl-beta-methylcholine (methacholine) bromide, in daily doses of 0.25 Gm. orally, induced improvement in function but brought about no change in the anatomic appearance of the esophagus in a patient with cardiospasm.[20] Follow-up study of 45 patients with cardiospasm who had been treated with forced dilatation, the period of observation extending from one-half year to seven years, indicated that 30 were completely or almost completely well; 7 were decidedly improved, 7 slightly improved, and 1 patient was not benefited by the treatment.[21] Pieri [22] treated 21 patients by so-called extramucosal cardiotomy, with excellent results in 18. Subsequent roentgen examination demonstrated the persistence of some dilatation of the esophagus but adequate peristalsis and normal emptying. Improvement followed resection of the left greater and lesser splanchnic nerves in a patient 22 years of age with symptoms of cardiospasm for three years; cardiospasm is thought to result from hypertonicity of the sympathetic nervous system.[23] Treatment by cardioesophageal myotomy is described by Gild.[24]

Malignant Tumors.—Carcinoma of the esophagus is, by far, the commonest cancer of the alimentary tract in Bombay, India.[25]

The diagnosis of cancer proved to be correct in 50 consecutive smears of secretions from the esophagus and the cardia of the stomach.[26] In 24 the carcinoma was primary in the esophagus, and in 26 it was primary in the cardia. The esophagoscopic biopsy was negative for cancer in 8 cases in which the smear was positive. The cytologic smear proved to be of more value in the diagnosis of carcinoma of the cardia than in that of carcinoma of the esophagus.

In a series of 277 patients metastases were present at the time of operation in 57.4 per cent.[27] Squamous cell carcinoma was the most frequent type of tumor histologically (60.6 per cent).

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20. Cattan, R.; Frumasan, P., and Attal, C.: Un cas de mégaoesophage traité par le bromure d'acétyl B methylcholine, Semaine d. hôp. Paris **23**:2911, 1947.

21. Gjertz, A. A.: Treatment of Achalasia Cardiae (So-Called Cardiospasm) by Forced Dilatation, Nord. med. **39**:1495, 1948.

22. Pieri, G.: La cura chirurgica del cardiospasmo, Arch. ital. mal. app. diger. **14**:326, 1948.

23. Bombi, G.: Contributo al trattamento neurochirurigico del megaesofago, Arch. ital. mal. app. diger. **14**:351, 1948.

24. Gild, A.: Surgical Treatment of Cardiospasm: Cardio-Esophageal Myotomy, M. J. Australia **352**:658, 1948.

25. Borges, E. J.: The Early Diagnosis and Treatment of Cancer of the Alimentary Tract, Indian J. M. Sc. **2**:223, 1948.

26. Anderson, H. A.; McDonald, J. R., and Olsen, A. M.: Cytologic Diagnosis of Carcinoma of the Esophagus and Cardia of the Stomach, Proc. Staff Meet., Mayo Clin. **24**:245, 1949.

27. Raven, R. W.: Carcinoma of the Esophagus: A Clinico-Pathological Study, Brit. J. Surg. **36**:70, 1949.

An operation in which the stomach is mobilized and anastomosed to the cervical portion of the esophagus is suggested for treatment of carcinoma of the esophagus in the superior mediastinum; in the patient described, death after operation was thought to be due to profound physiologic disturbances, possibly from vagal stimulation.[28] An operative technic for resection of neoplasms of the middle and lower thirds of the esophagus is described, using both a left upper abdominal and a right transthoracic approach through the bed of the seventh rib.[29] A carcinoma of the upper part of the esophagus with its upper border extending into the base of the neck was removed by an operative procedure in which the stomach is brought up into the chest and placed in a subcutaneous tunnel enlarged by removal of the medial half of the clavicle and the underlying first rib to meet the short, high-lying proximal esophageal segment; recovery was uneventful, and the patient subsequently gained weight and strength.[30] A squamous cell carcinoma of the esophagus in a woman 53 years old was removed successfully by a three stage esophagectomy, with presternal subcutaneous transposition of the stomach.[31] A carcinoma of the cervical part of the esophagus was treated by one stage total esophagectomy and pharyngogastrostomy; death occurred on the sixth postoperative day from a massive pulmonary embolus arising in the right iliac veins. The anastomosis in the cervical region was intact; there was no evidence of residual carcinoma.[32] An extensive muscular defect of the middle thoracic portion of the esophagus, after removal of a leiomyoma, was covered by a pedicled flap of pulmonary tissue.[33]

Experimental Esophageal Resection.—Resection of one third of the lower part of the esophagus, with end to end anastomosis, in 24 dogs resulted in 33 per cent mortality, regardless of approach or variation in technic.[34]

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28. Garlock, J. H.: Resection of Thoracic Esophagus for Carcinoma Located Above Arch of Aorta: Cervical Esophagogastrostomy, Surgery **24**:1, 1948.

29. Macmanus, J. E.: Combined Left Abdominal and Right Thoracic Approach to Resection of Esophageal Neoplasms, Surgery **24**:9, 1948.

30. Sweet, R. H.: Carcinoma of the Superior Mediastinal Segment of the Esophagus, Surgery **24**:929, 1948.

31. Taylor, H.: Further Report on the Operation of Esophagectomy with Presternal Esophago-Gastrostomy, Brit. J. Surg. **36**:419, 1949.

32. Shefts, L. M., and Fisher, A.: Carcinoma of the Cervical Esophagus with One-Stage Total Esophageal Resection and Pharyngogastrostomy, Surgery **25**:849, 1949.

33. Nissen, R.: Bridging of Esophageal Defect by Pedicled Flap of Lung Tissue, Ann. Surg. **129**:142, 1949.

34. Parker, E. F., and Brockington, W. S.: Esophageal Resection with End-to-End Anastomosis: Experimental and Clinical Observations, Ann. Surg. **129**:588, 1949. Swenson, O., and Clatworthy, H. W.: Partial Esophagectomy with End to End Anastomosis in the Posterior Mediastinum, Surgery **25**:839, 1949.

HIATUS HERNIA

Two thirds of 24 patients with hiatus hernia were overweight; 7 had been treated for coronary heart disease, 5 for disease of the gallbladder and 7 for peptic ulcer.[35]

Brick [36] noted 308 hiatus hernias among 3,448 patients undergoing routine roentgenologic study with barium sulfate solution. Associated gastrointestinal lesions were observed in 20 per cent, the most frequent lesion being duodenal ulcer. Evidence of organic heart disease was noted in approximately two thirds of 57 patients. Hiatus hernia may produce pain referred through reflex autonomic pathways to the wall of the chest and the left arm.[37]

Esophageal hiatus hernia may be complicated by inversion of the stomach.[38]

Treatment.—Merendino and his associates [39] describe a new method of repair of paraesophageal and hiatus hernias.

STOMACH

Gastric Secretion.—Experimental Observations: Crane, Davies and Longmuir [40] measured the potential difference, resistance, electrical power production and rate of acid secretion of isolated frog gastric mucosa with a special apparatus. The secretory side of frog gastric mucosa was negative with respect to the nutrient side in an external circuit. During acid secretion the potential difference was decreased and the resistance increased. Unstimulated frog gastric mucosae could send a current around an external circuit, producing a maintained elec-

35. Richards, G. G., and Crockett, K. A.: Hiatus Hernia, Arch. Surg. **58**:411 (April) 1949.

36. Brick, I. B.: Incidence of Hiatus Hernia and Associated Lesions Diagnosed by Roentgen Ray, Arch. Surg. **58**:419 (April) 1949.

37. Master, A. M.; Dack, S.; Stone, J., and Grishman, A.: Differential Diagnosis of Hiatus Hernia and Coronary Artery Disease, Arch. Surg. **58**:428 (April) 1949.

38. Marks, J. H.: Esophageal Hiatus Hernia with Inversion of the Stomach, Am. J. Roentgenol. **60**:63, 1948. Chaumerliac, J.; Chaumerliac, H. J., and Barrier, J. A.: Hernie diaphragmatique avec volvulus de l'estomac, Arch. d mal. de l'app. digestif **37**:711, 1948. Kidd, H. A.: Two Cases of Volvulus of the Stomach in a Diaphragmatic Hernia, Brit. J. Surg. **36**:50, 1949. Carter, B. N., and Giuseffi, J.: Strangulated Diaphragmatic Hernia, Ann. Surg. **128**:210, 1948. Dugan, D. J., and Samson, P. C.: Strangulation of the Stomach and Traumatic Diaphragmatic Hernia, J. Thoracic Surg. **17**:771, 1948.

39. Merendino, K. A.; Varco, R. L., and Wangensteen, O. H.: Displacement of the Esophagus into a New Diaphragmatic Orifice in the Repair of Para-Esophageal and Esophageal Hernia, Ann. Surg. **129**:185, 1949.

40. Crane, E. E.; Davies, R. E., and Longmuir, N. M.: Relations Between Hydrochloric Acid Secretion and Electrical Phenomena in Frog Gastric Mucosa, Biochem. J. **43**:321, 1948.

trical power output of the order of 1 microwatt per milligram of dry weight without appreciable polarization. About 10 per cent of the metabolic energy was thereby canalized into electrical energy. Based on these and other results, an electron-cycle mechanism of acid secretion is suggested, in which H atom and electron transport systems are coupled to produce a net separation of H^+ and OH^- ions in the pericanalicular zone of the oxyntic cells. The energy required is obtained from aerobic metabolism. Four of eight gastric mucosae of frogs, not initially secreting acid, commenced to secrete when an enhancing current was passed through them. No other membranes examined (esophageal, pyloric, duodenal and rectal mucosae, frog skin, cellophane® and dead gastric mucosa) produced hydrochloric acid with any currents applied.[41]

According to Terner,[42] diffusion of H^+ ions can occur through living isolated gastric mucosa. The quantitative significance of diffusion in normal mucosa remains uncertain, however. An apparatus, consisting of a constant pressure manometer, a modified Warburg cup and a stopper with a graduated capillary side tube, was used to study simultaneously the rates of fluid secretion and of respiration by isolated gastric mucosa.[43] Secretion occurred against opposing pressures of at least — 120 mm. Brodie solution and was generally independent of the magnitude and direction of the applied pressures. Histamine increased the rate of secretion and of respiration of the gastric mucosa. Thiocyanate strongly inhibited the rate of hydrochloric acid secretion. The data are interpreted as indicating that the energy for the movement of water across acid-secreting gastric mucosa is derived not from the difference in hydrostatic pressure between the blood and the gastric juice but from aerobic metabolism within the oxyntic cells. It was found by two methods in which an external battery is connected in series with the stomach that the average electrical energy production of the stomach of the dog was 38 and 28 microwatts per cubic centimeter, respectively, values definitely less than the minimum free energy necessary for the production of hydrochloric acid.[44]

Patterson and Stetten[45] offer a hypothesis for the formation of hydrochloric acid in the stomach, predicated on two basic assumptions:

41. Crane, E. E.; Davies, R. E., and Longmuir, N. M.: The Effect of Electric Current on HCl Secretion by Isolated Frog Gastric Mucosa, Biochem. J. **43**:336, 1948.

42. Terner, C.: Diffusion of Hydrogen Ions Through Isolated Gastric Mucosa, Biochem. J. **43**:xli, 1948.

43. Davies, R. E., and Terner, C.: The Effects of Applied Pressure on Secretion by Isolated Amphibian Gastric Mucosa, Biochem. J. **44**:377, 1949.

44. Rehm, W. S., and Hokin, L. E.: Ability of the Stomach to Produce Electrical Energy, Am. J. Physiol. **154**:148, 1949.

45. Patterson, W. B., and Stetten, D., Jr.: A Study of Gastric HCl Formation, Science **109**:256, 1949.

that the H ions of the gastric juice are made available from the reduction of pyridine nucleotide, and that the enzymes of the oxidation-reduction systems in the parietal cells are arranged in successive stratums.

Utilizing the Warburg apparatus, Davenport and Jensen [46] carried out interesting studies on the secretion of acid by the excised stomachs of adult white mice. The observations are summarized as follows:

Acid accumulates in the lumen of the excised mouse stomach incubated at 38° C. in phosphate buffer. The difference between the total acid accumulating and the sum of the lactic and carbonic acids present is inorganic acid secreted by the mucosa.

The acid secretion is enhanced by the presence of glucose and carbaminoylcholine. It is unaffected by pretreatment of the mice with tetraethyl ammonium bromide and is slightly depressed by 1 mg. % histamine.

The acid secretion is inhibited by thiocyanate ions, epinephrine and 25 mg. % thiophene-2-sulfonamide. It is only slightly depressed by 12.5 mg. % thiophene-2-sulfonamide or 200 mg. % sulfanilamide.

Enterogastrone can inhibit acid secretion in the excised mouse stomach.

The acid secretion is reduced when potassium, calcium or magnesium is omitted from the buffer solution and when the concentration of magnesium is 2.4 mM/l. A potassium concentration of 12 mM/l. has no effect.

Alkali accumulates in the external fluid as acid accumulates in the lumen of the stomach.

The rate of acid secretion by the mouse stomach in vitro was noted to be poorly correlated with the dry weight of the stomach, the amount of carbonic anhydrase present, pyruvic acid metabolism and urease activity. Carbaminoylcholine did not stimulate acid secretion; ethyl alcohol and peptone had no effect, and atropine inhibited secretion. The stomach was observed not to contain a conspicuously active system for deaminating amino acids.[47]

On the basis of experiments carried out chiefly by Unäs, Kahlson [48] presents the thesis that gastrin is contained in the pyloric mucosa and, in man and pigs, in the duodenum as well. This agent is liberated by vagal impulses or when chemical substances, such as food, come in contact with the mucosal regions concerned. The liberated gastrin is carried by the blood to the fundic mucosa, where it causes some change so that histamine is liberated in quantities sufficient to stimulate the parietal cells. In this concept gastrin constitutes a common factor in the nervous, gastric and intestinal phases of acid gastric secretion.

46. Davenport, H. W., and Jensen, V.: The Secretion of Acid by the Mouse Stomach in Vitro, Gastroenterology **11**:227, 1948.

47. Davenport, H. W., and Jensen, V.: Observations on the Secretion of Acid by the Mouse Stomach in Vitro, Gastroenterology **12**:630, 1949.

48. Kahlson, G.: The Nervous and Humoral Control of Gastric Secretion, Brit. M. J. **2**:1091, 1948.

Effect of Methacholine: In 21 dogs given 15 to 35 mg. of methacholine (mecholyl®) chloride in aqueous solution subcutaneously or methacholine chloride in a beeswax-mineral oil mixture intramuscularly, acid secretion was stimulated in most instances and the secretory response was prolonged in at least one third of the animals.[49] The watery mucoid character and the extremely high acidity of this secretion closely resembled that obtained by stimulation of the vagi in dogs. The failure to elicit a secretory response to the same dose of methacholine chloride or histamine after the initial secretion had declined suggested that the secretory apparatus had become refractory to further methacholine chloride or histamine stimulation.

Effect of Acetylcholine: Introduced into the left gastric artery (region of the lesser curvature), acetylcholine causes a secretion of low acidity but containing large quantities of mucus and pepsin; for the most part, free hydrochloric acid is absent and the total chloride is low. Injected into the gastrosplenic artery (body of stomach along the greater curvature), acetylcholine causes an abundant flow of an alkaline secretion, containing variable amounts of dissolved, opalescent mucus but no pepsin; the total chloride varies between 94.5 and 144.3 milliequivalents per liter. Injection into the right gastroepiploic artery (pyloric region) stimulates a secretion of clear alkaline mucus. It is concluded that the alkaline secretion evoked by injections of acetylcholine into the gastrosplenic artery comes from the inner one third of the glands of the body of the stomach along the greater curvature, the chief cells of the neck and possibly the surface epithelium contributing to this secretion.[50]

Effect of Sedation, Anesthesia and Fear: The effect of 80 barbiturates, thiobarbiturates and thiourea derivatives on gastric secretion was studied in unanesthetized cats with permanent gastric fistulas.[51] Ethyl-3:3-dimethylallyl barbiturate and ethyl-1:3-dimethyl-1-butenyl barbiturate caused a profuse gastric secretion, the volume and acidity being as great or greater than that evoked by histamine; 1-methylbutylethylacetyl thiourea inhibited the stimulating effect of insulin without causing any other untoward effect. Other substances did not inhibit such secretion, unless given in doses large enough to cause ataxia or anesthesia. The commonly used barbiturates were without effect on gastric secretion until near-anesthetic doses were used.

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49. Wener, J.; Karp, D., and Hoff, H. E.: The Effect of Mecholyl in Beeswax on Gastric Secretion, Gastroenterology **11**:923, 1948.

50. Morton, G. M., and Stavraky, G. W.: A Histo-Physiological Study of the Effect of Intraarterial Injection of Acetylcholine upon the Gastric Mucosa of the Dog, Gastroenterology **12**:808, 1949.

51. Noble, R. L.: The Stimulation and Inhibition of Gastric Secretion in Cats by Barbiturate and Thiourea Derivatives, Canad. M. A. J. **60**:55, 1949.

Anesthesia induced with chloralose and chloralose and methane caused a profuse secretion of acid gastric juice in dogs with gastric fistulas who were not subjected to trauma at the time of anesthetization.[52] Urethane, thiopental (pentothal®) sodium and, to a much lesser degree, pentobarbital sodium (nembutal®) anesthesia also evoked the secretion of varying amounts of gastric juice of high acidity under similar conditions. The secretion accompanying anesthesia induced with the chloralose and urethane mixture was found to approach a p_H of 0.9 and to possess minimal amounts of pepsin and visible mucus, which resembled histamine-stimulated secretion. It was completely abolished by the traumatic procedure of preparing the gastric fistula at the time of the experiment and, at times, was completely prevented by slight mechanical manipulation of the vagi in the neck. The secretion was not associated with a reduced blood sugar level but was regularly abolished by administration of atropine. It was greatly reduced or unobtainable in vagotomized dogs.

A modified conditioning procedure was used to develop a state of chronic fear in 7 dogs.[53] Six of the dogs were considered to be chronically fearful and to have increased gastric acidity, increased gastric emptying and increased variability of both nonresting and resting heart rates. Removal of the animals from the experimental environment or omission of the reenforcing pain stimulus resulted in recovery of these changes in behavior and gastric and cardiac function. Gross and histologic examination of the stomach and duodenum showed no evidence of pathologic involvement of tissue in any of the animals. In this respect, the author calls attention to the relatively short duration of the experiments (six to eight months).

The gastric secretory response to the instillation of 300 ml. of 0.5 per cent hydrochloric acid solution was investigated thirty times in 8 subjects.[54] In six experiments duodenal regurgitation was prevented by constant duodenal suction. In 14 experiments phenolsulfonphthalein was added to the instilled solution, and the amount of dilution was measured. On the average, the decrease in concentration of the dye was the same as that of the acid. It is concluded that instillation of acid into the human stomach stimulates one or more secretions the net effect of which is to reduce the acidity by dilution.

Clinical evidence is presented to show that parietal cell secretion is not abolished in chronic severe acidosis of renal origin or in the acidosis

52. Shachter, M.: Anesthesia and Gastric Secretion, Am. J. Physiol. **156**:248, 1949.

53. Mahl, G. F.: Effect of Chronic Fear on the Gastric Secretion of HCl in Dogs, Psychosom. Med. **11**:30, 1949.

54. Bermak, G. E., and Doupe, J.: The Gastric Response of Man to an Acid Test Meal, Canad. J. Research **27**:90, 1949.

of diabetes; histamine is capable of stimulating the parietal cell, regardless of whether acidosis is induced before or after histamine is given.[55]

Creatine and Creatinine in Gastric Juice: The concentrations of creatinine and creatine in the gastric juice obtained after histamine stimulation were the same in normal subjects and in patients with gastritis, carcinoma or peptic ulcer.[56] There was no correlation between the levels of creatinine and creatine in the gastric juice and those in the blood or with the free or total acidity.

Effect of Caffeine and Theophylline: The magnitude and duration of histamine stimulation of gastric secretion in the anesthetized cat were increased after the intravenous injection of caffeine in doses ordinarily not stimulating the gastric secretion; a similar but less consistent potentiating effect was noted with theobromine and theophylline.[57] Theophylline given orally or intravenously increases the secretion of hydrochloric acid in the human stomach.[58] The volume of secretion was greatest fifteen minutes after injection of aminophylline in doses of 0.5 Gm. in 10 cc. of saline solution and forty-five minutes after administration of the same quantity in 200 cc. of water by stomach tube.

Effect of Tetraethylammonium Chloride: Tetraethylammonium chloride given intravenously in doses of 400 to 600 mg. abolished all gastric motility within five minutes in 23 patients studied. In similar studies the drug reduced basal gastric secretion by 88 per cent for forty-five to sixty minutes and decreased the gastric acid response to continuous intravenous infusion of a small dose of histamine phosphate by 70 per cent.[59] Parenteral administration of tetraethylammonium chloride produces a temporary cessation of all forms of motility of the stomach and small bowel as examined roentgenologically.[60] Neither atropine nor epinephrine alone decreases motility to a similar extent, but previous injection of either magnifies the gastrointestinal inhibition following small doses of tetraethylammonium chloride. The drug reduces gastric acidity and secretory volume and blocks the secretory response to insulin hypoglycemia. Relief of gastrointestinal pain is frequently noted; visceral

55. Logan, V. W.: Is Parietal Cell Secretion Inhibited by Acidosis? Gastroenterology **12**:671, 1949.

56. Russo, F., and Marrazza, P.: Creatine Bodies in the Gastric Juice of Normal and Gastropathic Subjects, Fisiol. e med. **15**:301, 1947.

57. Wood, D. R.: Caffeine and Gastric Secretion, Brit. M. J. **2**:283, 1948.

58. Krasnow, S., and Grossman, M. I.: Stimulation of Gastric Secretion in Man by Theophylline Ethylenediamine, Proc. Soc. Exper. Biol. & Med. **71**:335, 1949.

59. Zweig, M.; Steigmann, F., and Meyer, K. A.: The Effect of Tetraethylammonium Chloride on Gastric Motility and on the Unstimulated and Histamine-Stimulated Gastric Secretion, Gastroenterology **11**:200, 1948.

60. Neligh, R. B.; Holt, J. F.; Lyons, R. H.; Hoobler, S. W., and Moe, G. K.: Effects of Tetraethylammonium Chloride on the Human Gastrointestinal Tract, Gastroenterology **12**:275, 1949.

afferent painful stimuli are not blocked. Mydriasis, dryness of the mouth and orthostatic hypotension interfere with administration of the drug over long periods.

Effect of Enterogastrone: The effect of enterogastrone preparations on gastric secretion was studied in 20 human subjects and 4 dogs with Heidenhain pouches.[61] With doses large enough to produce toxic reactions in the dogs the output of acid was decreased. Two hundred milligrams given intramuscularly did not affect significantly the gastric secretory response to a double histamine test in human subjects. Enterogastrone extracts given orally to 14 volunteers in doses as large as 400 mg. intramuscularly and 18 Gm. orally did not significantly affect the gastric secretory response to a modified Ewald test meal.

Effect of Tween® 20: Tween® 20 (a polyoxyalkylene ether of partial lauric acid esters) produces urticaria and stimulates gastric secretion when injected intravenously in a dose of 0.8 mg. per kilogram of body weight in dogs with gastric pouches.[62] Pretreatment with diphenhydramine (benadryl®) hydrochloride prevents or reduces in most instances the urticariogenic and secretory effects of this wetting agent.

Miscellaneous Observations: In 106 tests performed after intravenous injection of protein hydrolysates, increased gastric acidity was obtained in 55 per cent; gastric motility was unaffected.[63] Neither vagotomy nor thoracic sympathectomy and splanchnicectomy inhibited the gastric response. Atropine sulfate in small doses given intravenously did not reduce the stimulated gastric acidity; a larger dose, 1/60 grain (1.08 mg.), definitely decreased the acid response.

Orange and tomato juices exert a slight buffering effect on the gastric secretion, followed after half an hour by a stimulant influence.[64] Gastric secretion was measured before and after a series of blood transfusions in 11 patients with anemia of varied origin; the acidity increased in most of them. No effect was observed in patients with achlorhydria.[65]

Suppression of Gastric Acidity with P^{32}: After the secretory response of Heidenhain pouches of the stomach to histamine had been determined

61. Feyayorni, R. R.; Code, C. F., and Morlock, C. G.: The Effect of Enterogastrone Concentrates on Gastric Secretion in Human Beings, Gastroenterology **11**:730, 1948.

62. Grossman, M. I., and Robertson, C. R.: Stimulation of Gastric Secretion by Urticariogenic Wetting Agent (Tween 20) and Its Inhibition by Benadryl, Proc. Soc. Exper. Biol. & Med. **68**:550, 1948.

63. Zweig, M.; Meyer, K. A., and Steigmann, F.: Effect of Intravenous Protein Hydrolysates on the Stomach, Gastroenterology **12**:586, 1949.

64. Yeagley, J. D., and Cayer, D.: Changes in Gastric p_H Following the Administration of Fruit Juice to Patients with Peptic Ulcer, North Carolina M. J **9**:555, 1948.

65. Pulitano, E.: Azione delle ripetute trasfusioni di sangue sulla secrezione gastrica, Minerva med. **1**:591, 1948.

in dogs, P^{32} was applied topically to the mucosal lining of the pouches by means of a specially devised applicator.[66] The beta radiation was followed after a few days by a decrease in total secretion, as well as a decrease in quantity and concentration of hydrochloric acid, in the pouches of all 5 dogs studied; anacidity occurred in 2 of the group. There were no changes in blood count, weight or general condition of the animals which could be attributed to the radiation. In one dog the gastric acidity returned three months after irradiation. When the animal was killed two weeks later, autopsy demonstrated an ulcer of the pouch mucosa at the site of previous biopsy.

Hormonal Factors: Dogs deprived of ovaries do not excrete urogastrone in the urine in the quantities observed in normal dogs. If thyroidectomy is combined with oophorectomy, the inhibitory substance appears in the extracts in approximately normal quantities. After thyroidectomy alone, the urine extract induces a pronounced inhibition of gastric secretion. Urine extracts from oophorectomized dogs do not influence histamine-stimulated gastric secretion as do extracts of normal urine.[67]

Moderate doses of diethylstilbestrol produced some atrophy and desquamation of mucosa, particularly of the lesser curvature of the stomach.[68] Large doses caused considerable mucosal atrophy, disappearance of glandular elements and increase in fibrous tissue. Regeneration occurred with cessation of injections. Similar changes were not observed when other hormones, progesterone, testosterone, desoxycorticosterone and extract of the anterior lobe of the pituitary, were given concurrently. The gastric secretory response to histamine was diminished or absent in the majority of 20 patients with hypothyroidism; a hypochromic anemia often was present concomitantly.[69]

Effect of Pyrexia, Infections and Helminths: Experimentally induced pyrexia in animals invariably was accompanied with achlorhydria; the secretory response to histamine was normal in 12 patients with acute infections.[70]

66. Simon, N.: Suppression of Gastric Acidity with Beta Particles of P^{32}, Science **109**:563, 1949.

67. Kaulsbersz, J.; Patterson, T. L.; Sandweiss, D. J., and Saltzstein, H. C.: The Effect of Urine Extract from Oophorectomized Dogs on Gastric Secretion, Rev. Gastroenterol. **16**:254, 1949; The Effect of Urine Extract from Thyroidectomized Dogs on Gastric Secretion, ibid. **16**:257, 1949.

68. De Busscher, G.: L'influence de très fortes doses de stilbœstrol seul et de stilbœstrol associé à d'autres hormones sur l'estomac du lapin, Acta gastro-enterol. belg. **12**:141, 1949.

69. Bastenie, P. A., and Kowalewski, K. P.: Gastrointestinal Disturbances in Insufficiency of the Thyroid Gland, Gastroenterologia **74**:225, 1949.

70. Friis-Hansen, B.: Gastric Secretion During Acute Infections, Nord. med. **40**:2094, 1948.

Anacidity or decreased acidity was observed in 44 of 62 patients with infection with Ascaris, in 10 of 14 having ancylostomiasis and in all of the 10 showing infection with Trichuris trichiura (Trichocephalus trichiuris); gastric secretion returned to normal after removal of the worms.[71]

Physiologic Studies of Gastric Secretion in Human Subjects: In a study of 27 patients, continuous gastric secretion was noted (2 to 8 ml. per hour).[72] No difference in the effect on secretion was observed between real and sham feeding. Bilateral vagotomy completely abolished the reflex psychic phase of gastric secretion; however, a spontaneous, usually rhythmic secretion (up to 120 ml. per hour) without free acid was noted. The histamine effect in these cases was slight; the effect of alcohol also was abolished or was very slight, attributable to intracellular changes in the gastric mucosa. In dogs, morphologic changes not differing from gastritis were observed after bilateral vagotomy.

Direct observations of the interior of the stomach were made through a large gastrostomy opening in a 21 year old Negro woman.[73] A cyclic motility was observed; the interval between cycles and the magnitude of contractions varied considerably. Two types of contraction were seen, a basic kneading type and a peristaltic type. Under standard conditions, with the patient fasting and in a happy and cooperative mood, a moderately active, secreting stomach with relatively red mucosa was observed. Anger, resentment, fear and anxiety were associated with decreased motility and output of acid, and with blanching of the mucosa. Mechanical stimulation in the region of the cardiac sphincter induced heartburn, nausea, retching and a reflux of bile-stained secretion. Painful stimuli increased gastric motility but had little effect on secretion or the color of the mucosa. Menstruation and periods of sleep had little effect on the observed behavior of the stomach. The absence of hypersecretion and hypermotility under conditions of sustained emotional tension in this patient was in contrast to their presence in male patients previously studied. In the same patient intravenous administration of a 5 per cent solution of hydrolyzed protein or crystalline amino acids in 5 per cent dextrose solution decreased gastric motility and secretion. Inhibitory effects on gastric function were not observed during injections of 10 per

71. Astraldi, F. P.: Il comportamento della secrezione gastrica in alcune parassitosi da elminti, Fisiol. e med. **16**:19, 1948.

72. Razentov, I. P., and Ugpensky, U. N.: Material for the Study of the Activity of the Glands in the Stomach in Humans with Fistulae of the Stomach, Esophagus and Small Intestine and Intact or Severed Vagus Nerves, Physiolog. V. **33**:603, 1947.

73. Crider, R. J., and Walker, S. M.: Physiologic Studies on the Stomach of a Woman with a Gastric Fistula, Arch. Surg. **57**:1 (July) 1948; Effect of Intravenously Administered Amino Acids on the Stomach of a Woman with a Gastric Fistula, ibid. **57**:10 (July) 1948.

cent dextrose solution with or without sodium chloride or of isotonic solution of sodium chloride.

Neutral Red Excretion Test.—The quantitative aspects of the excretion of neutral red by the liver, kidneys and stomach were studied in acute experiments on dogs under anesthesia induced by pentobarbital sodium. The liver plays a predominant part in the excretion of the dye. The resting stomach failed to excrete any dye, and only a small portion of the injected material was excreted when gastric juice was secreted at a high rate for several hours.[74] Sevitt and Jepson [75] conclude that the neutral red excretion test is of no value in the differential diagnosis of gastric disease.

Gastric Mucin.—Evidence is presented to indicate that the dissolved mucin of human gastric contents is not an entity but a mixture of at least two viscous components which differ widely in many physical and chemical respects. These are dissolved gastric mucoprotein and dissolved gastric mucoproteose. The mucoprotein is a product of mucoid chief cells of the gastric glands of the body and fundus. Dissolved gastric mucoproteose contains a protein moiety showing the characteristics of a proteose, as well as a viscous compound related to mucopolysaccharides. There is evidence that the dissolved mucoproteose of the filtered gastric juice is mainly derived from the digestion of the mucoid of the mucus of gastric surface epithelium.[76] A routine method for separation and quantitative determination of three main components of the gastric mucin is described, based on (*a*) separation of the fluid gastric juice and visible mucus; (*b*) removal of contaminants by means of trichloracetic acid precipitation; (*c*) precipitation of the total dissolved mucin complex from the trichloracetic acid filtrate with acetone at 40 C. (104 F.);

74. Kolm, R.; Komarov, S. A., and Shay, H.: Quantitative Determination of Neutral Red in Gastric Juice and Gastric Contents, Rev. canad. de biol. **8**:262, 1949. Komarov, S. A.; Kolm, R., and Shay, H.: The Excretion of Neutral Red by the Liver, Kidneys and Stomach, ibid. **8**:285, 1949.

75. Sevitt, S., and Jepson, R. P.: The Gastric Neutral-Red Excretion Test, J. Clin. Path. **1**:217, 1948.

76. Glass, G. B. J., and Boyd, L. J.: The Three Main Components of the Human Gastric Mucin: Dissolved Mucoproteose, Dissolved Mucoprotein, and Mucoid of the Gastric Visible Mucus: I. Differentiation: Some Physical and Chemical Characteristics; Classification, Gastroenterology **12**:821, 1949; II. Method for Separation and Quantitative Determination of Each Mucous Component of the Gastric Content, ibid. **12**:835, 1949; III. Preliminary Data on Physiological and Clinical Significance of Separate Quantitative Determination of the Dissolved Mucoproteose and Dissolved Mucoprotein in the Gastric Juice of Man, ibid. **12**:849, 1949. Glass, G. B. J.; Boyd, L. J.; Heisler, A., and Drekter, I. J.: Studies on Dissolved Mucin of the Gastric Juice: III. Heterogeneity of the Gastric Dissolved Mucin and Its Differentiation and Separation into 2 Main Factors: Dissolved Mucoproteose and Dissolved Mucoprotein, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **2**:8, 1948.

(*d*) fractionation of the total dissolved mucin complex into dissolved mucoproteose and dissolved mucoprotein by dissolution of the mucin precipitate in dilute alkali and reprecipitation of the mucoprotein fraction from this solution with dilute hydrochloric acid at a *p*H below 4; (*e*) quantitative estimation of each of the fractionated mucous substances on the basis of its tyrosine content, after alkaline hydrolysis by means of the Folin-Ciocalteu colorimetric reaction with phosphotungstic-phosphomolybdic phenol reagent, using tyrosine solution as a standard.

The highest values of dissolved mucoproteose are found in anacid fasting fluid gastric contents and, usually, in patients having gastritis, chronic alcoholism or disturbances in motility of the vagotomized stomach. Its concentration decreases after alcoholic or histaminic stimulation of the stomach and usually increases following the intravenous injection of insulin. The secretion of dissolved mucoprotein is related in some way to the secretion of hydrochloric acid. Relatively high values are observed in the fasting gastric content of the hyperacid, irritable stomach of duodenal ulcer and in some instances of gastritis with normal or increased acidity. The concentration of dissolved mucoprotein increases as much as fourfold after the intravenous administration of insulin. This effect is abolished or greatly decreased in the human vagotomized stomach. In patients with a subtotally resected stomach, the intravenous injection of insulin causes a rise in the concentration of mucoprotein and mucoproteose in the gastric content as distinct as that observed in the intact stomach. The authors suggest that an increase in mucoprotein and no response in acidity after insulin administration would indicate that the negative response of acidity was due to resection and not to vagotomy. The negative response of both acidity and of dissolved mucoprotein content would indicate complete section of the vagi.

A modification of Tollens' naphthoresorcinol reaction for glucuronic acid, with the use of a photoelectric colorimeter, has proved to be a reliable method of estimating the concentration of mucin in gastric juice.[77] The lowest concentrations were noted following histamine administration, the highest in the alkaline mucus of a fasting stomach and intermediate values after sham feeding. The volumes, acidity and total output of mucus in the gastric secretion, under fasting conditions and following stimulation by histamine, were studied in 56 patients with various diseases and in 13 controls.[78] The amount of reducing substances after acid hydrolysis was taken as a measure of the total mucous content. Normal controls and patients with peptic ulcer showed similar

77. Siplet, H.; Komarov, S. A., and Shay, H.: The Estimation of Mucin in Gastric Juice, J. Biol. Chem. **176**:545, 1948.

78. Weiden, S.: Some Observations on the Secretion of the Stomach with Special Reference to Mucus, M. J. Australia **2**:81, 1949.

values for volume, acidity and total mucous secretion. There was a depression of gastric secretion in chronic gastritis.

Pepsin and Peptic Activity.—A new phototurbidimetric method for determination of pepsin is described by Friedman.[79] A colorimetric procedure for determining the proteolytic activity of gastric and duodenal juice is based on the observation that the digestion of a solution of azoalbumin by a dilution of the digestive juice produces colored reaction products which are soluble in trichloracetic acid; the color intensity of the trichloracetic acid filtrate of the digested substrate solution is a function of the concentration of proteolytic enzymes.[80] The specific inhibitory power of an insoluble polyamine resin on peptic activity was increased by the addition of small amounts of sodium alkyl sulfate.[81] Peptic activity also was inhibited by such substances as charcoal, calcium phosphate, various proteins and proteoses and colloidal aluminum hydroxide.

Gastric Motility and Emptying.—The effect of depressants of the central nervous system, chloral hydrate, bromisovalum (bromural®), paraldehyde and pentobarbital on the emptying time of the human stomach was investigated.[82] With chloral hydrate the average value for emptying time was normal; however, in 3 of the 12 subjects there was a significant increase in gastric motility. Bromisovalum and paraldehyde had no effect on the average emptying time, but motility was increased in occasional subjects. Pentobarbital significantly decreased the emptying time in the majority of subjects. There appeared to be no correlation between sedative action and the effect on the motility of the stomach. In dogs, gastric emptying was not affected significantly by barbiturates (amobarbital [amytal®], secobarbital [seconal®], pentobarbital [nembutal®]) and was delayed only slightly by meperidine (demerol®) and methadone (AN 148).[83] Morphine and methadone in large doses produced pronounced delay in the passage of the test meal; scopolamine in five doses given over five hours definitely prolonged the emptying time and, when added to other medicaments, supplemented their effects.

79. Friedman, M. H. F.: Phototurbidimetric Determination of Pepsin, Exper. Med. & Surg. **6**:149, 1948.

80. Tomarelli, R. M.; Charney, J., and Harding, M. L.: The Use of Azoalbumin as a Substrate in the Colorimetric Determination of Peptic and Tryptic Activity, J. Lab. & Clin. Med. **34**:428, 1949.

81. Alpert, S., and Martin, G. J. A.: A Comparative Study of the Inhibitory Action of Chemical Agents on Peptic Activity, Am. J. Digest. Dis. **16**:10, 1949.

82. Northup, D. W., and Van Liere, E. J.: The Effect of Central Nervous System Depressants on the Emptying Time of the Human Stomach, J. Pharmacol. & Exper. Therap. **93**:208, 1948.

83. Chase, H. F.: The Role of Delayed Gastric Emptying Time in the Etiology of Aspiration Pneumonia, Am. J. Obst. & Gynec. **56**:673, 1948.

The effects of three synthetic antispasmodics, (*a*) diethylaminoethyl esters of fluorene-9-carboxylic acid (pavatrine®), (*b*) 9,10-dihydroanthracene-10-carboxylic acid and (*c*) xanthene-9-carboxylic acid, were compared with those of atropine in human subjects.[84] In doses producing side effects of equal intensity, the synthetic compounds produced longer depression of gastric motility than did atropine given intragastrically or intraduodenally. Atropine administered intragastrically induced greater depression of gastric secretion than did any of the synthetic drugs. Gastric motility is decreased by an excess of calcium and accelerated by a lowering of calcium or by an increase of potassium.[85]

Gastric Absorption.—Karel [86] notes that the absorptive ability, particularly as regards substances physiologically active in minute quantities, has been grossly underestimated.

Vascularization of Human Stomach.—Barclay and Bentley [87] injected bismuth oxychloride at a pressure of 150 mm. of mercury into the arteries of the stomach excised at operation (for duodenal ulcer) or removed from the cadaver; arteriographs of the gastric wall were made, and transverse sections of different areas of the wall were subjected to the technic of microarteriography. It was deduced that in the wall of the stomach there are arteriovenous anastomoses in the region of the submucous plexus of vessels, the opening of which excludes active circulation through the vessels of the mucous membrane. When the peritoneal cavity is opened and the stomach handled at operation, the shunt comes into play, and this condition persists in the excised stomach wall after the operation. There is some evidence indicating that the arteriovenous anastomoses in the stomach wall are under the control of the autonomic nervous system, for when the sympathetic outflow to the stomach is blocked by means of a spinal anesthetic the shunts do not open and injection of the stomach vessels reveals complete filling of the extensive blood supply of the mucous membrane.

Experimental Devascularization.—Devascularization of the stomach in dogs produces minimal histologic changes of focal atrophy and disappearance of parietal and chief cells in the superficial one third of the gastric mucosa.[88] Later, there is stromal fibrosis in a narrow zone

84. Higgins, J. R.; Schoen, A. M., and Knoefel, P. K.: The Effects of Some Synthetic Antispasmodic Agents on Human Gastric and Duodenal Functions, Gastroenterology **11**:508, 1948.

85. Bekaert, J.: Influence de la teneur en calcium et en potassium du liquide céphalorachidien sur les mouvements de l'estomac, Arch. internat. de pharmacodyn. et de thérap. **77**:54, 1948.

86. Karel, L.: Gastric Absorption, Physiol. Rev. **28**:443, 1949.

87. Barclay, A. E., and Bentley, F. H.: The Vascularization of the Human Stomach: A Preliminary Note on the Shunting Effect of Trauma, Brit. J. Radiol. **22**:62, 1949; Gastroenterology **12**:177, 1949.

88. Holm, B.; Boyarsky, S., and Morrione, T. G.: The Effect of Experimental Devascularization on Gastric Mucosa, Gastroenterology **12**:116, 1949.

beneath the surface epithelium. In the dog not enough atrophy of the secretory cells of the mucosa follows devascularization to provide histologic evidence for the occurrence of a "physiologic gastrectomy."

Nausea.—The nauseating effect of amigen® (protein hydrolysates) was thought to be due to its "disgusting taste." [89] Copper sulfate produced no nausea when allowed access only to the stomach, though it precipitated mucus and irritated the mucosa. Mechanical irritation of the gastric mucosa likewise failed to produce nausea. Ipecac proved to be nonirritating to the stomach and was observed to exert its emetic action only after reaching the duodenum; prior to the onset of nausea there was inhibition of gastric secretion and motor activity which outlasted nausea. Accompanying nausea was a simultaneous change in the pattern of motor activity, mainly characterized by an increase in tone.

Gastroscopy.—A new flexible gastroscope is described as essentially similar to the present flexible gastroscope, with an additional channel for an aspirating tube or biopsy forceps; a proximal thumb screw directs the biopsy forceps.[90] Satisfactory biopsies have been safely obtained in the small number of patients examined so far. Wood and his associates [91] describe a flexible gastric biopsy tube and the technic for its use. A total of 55 specimens has been obtained thereby in 83 attempts, without evidence of pain or hemorrhage. Chamberlin's [92] gastroscope has a longer rigid portion, controlled flexibility of the tip and a smooth metal tip.

Anacidity and Histologic Appearance of Stomach.—Two hundred and seventy-six gastric specimens surgically removed for various gastric and duodenal diseases were studied histologically.[93] The results of gastric analyses were correlated with the anatomic distribution of the parietal cells and the degree of gastritis present. Increases in the intensity of the chronic atrophic gastritis are associated with a proportionate decrease in the number of parietal cells. The production of hydrochloric acid is directly proportional to the number of normal-appearing parietal cells present in the mucosa of the fundus.

Fifty-four patients were studied to determine the relationship between gastric secretion and the histologic appearance of the mucosa of the

89. Wolf, S.: Studies on Nausea, Gastroenterology **12**:212, 1949.

90. Benedict, E. B.: An Operating Gastroscope, Gastroenterology **11**:281, 1948.

91. Wood, I. J.; Doig, R. K.; Motteram, R., and Hughes, A.: Gastric Biopsy: Report of 50 Biopsies Using a New Flexible Gastric Biopsy Tube, Lancet **1**:18, 1949.

92. Chamberlin, D. T.: Description of a New Gastroscope, Gastroenterology **12**:209, 1949.

93. Guiss, L. W., and Stewart, F. W.: Histologic Basis for Anacidity in Gastric Disease, Arch. Surg. **57**:618 (Nov.) 1948.

body of the stomach. Biopsies were taken by a flexible gastric biopsy tube; gastric ulcer and carcinoma were excluded.[94] In 18 patients with severe atrophy, achlorhydria with low total volume and low to absent pepsin were invariable. In the presence of a normal or nearly normal mucosa, the secretion usually was normal or "intermediate."

Anacidity–Gastroscopic Observations. — The correlation between maximum free acidity and the gastroscopic appearance of the gastric mucosa is not exact; achlorhydria occurred in only 5 per cent of patients with normal mucosa, in 2 per cent of patients with hypertrophic mucosa and in 30 per cent of patients with atrophic mucosa and superficial gastritis.[95]

Chronic Gastritis.—The incidence of symptoms of chronic gastritis in persons without roentgenologic evidence of disease and with a gastroscopically normal mucosa does not differ significantly from that observed in patients with atrophy of the gastric mucosa, chronic superficial gastritis and hypertrophic gastritis; an erosive gastritis, however, may produce ulcer-like distress.[96] Gastritis complicated by massive hemorrhage is recorded.[97] Berry and Cole [98] relate atrophy of the gastric mucosa to nutritional defects.

Irradiation Gastritis.—Moderate roentgen irradiation of the fundus and body of the stomach in man produces an acute transitory inflammation of the gastric wall.[99] This is characterized gastroscopically by hyperemia, hemorrhage, edema and adherent exudate and histologically by degenerative changes in the epithelial cells and lymph follicles, increased cellular infiltration and relatively minor changes in the blood vessels. Atrophy of the gastric mucosa often ensues and is uniformly present in patients with prolonged postradiation anacidity.

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94. Wood, I. J.; Doig, R. K.; Motteram, R.; Weiden, S., and Moore, A.: The Relationship Between the Secretions of the Gastric Mucosa and Its Morphology as Shown by Biopsy Specimens, Gastroenterology **12**:949, 1949.

95. Ricketts, W. E.; Kirsner, J. B., and Palmer, W. L.: The Secretory Response to Histamine in Individuals with a Normal and Abnormal Gastric Mucosa, Am. J. M. Sc. **217**:539, 1949.

96. Ricketts, W. E.; Palmer, W. L., and Kirsner, J. B.: "Chronic Gastritis": A Study of the Relation Between Mucosal Changes and Symptoms, Gastroenterology **12**:391, 1949.

97. Chipman, I. L., Jr.: Hemorrhage Associated with Gastritis (Review of Literature and Report of 2 Cases), U. S. Nav. M. Bull. **48**:253, 1948. Engel, G. C., and Singmaster, L.: Acute Diffuse Hemorrhagic Gastritis, Gastroenterology **12**:146, 1949.

98. Berry, L. H., and Cole, J. T.: Therapy of Chronic "Atrophic Gastritis" with 8 Years' Gastroscopic Control, J. A. M. A. **138**:485 (Oct. 16) 1948.

99. Ricketts, W. E.; Kirsner, J. B.; Humphreys, E. M., and Palmer, W. L.: Effect of Roentgen Irradiation on the Gastric Mucosa, Gastroenterology **11**:818, 1948.

Gastroscopic studies in 12 soldiers who had acquired postirradiation gastritis following intensive radiation therapy for malignant disease (tumor of the testis) demonstrated conspicuous edema with tubular deformity and fixation of the antrum, fixed patulousness of the pylorus and clean, deep chronic ulcers which healed without contracture. The correlation between the gastroscopic picture and the pathologic appearance of the resected specimens was fairly satisfactory. That which was taken for submucosal infiltration, however, proved to be mere edema. An unexpectedly large amount of fibrosis was noted.[100]

Syphilis of the Stomach.—Among 3,066 cases of peptic ulcer observed in sixteen years, 52 (1.7 per cent) were of syphilitic origin.[101] Decreased acidity or anacidity was noted in 42. Gastroscopy revealed shallow ulcers with irregular edges and smooth pink bases. The adjacent mucosa was hyperemic, but edema was not observed. Erosions often were seen along the lesser curvature and occasionally were the source of profuse hemorrhage. Treatment with arsphenamine produced considerable improvement, even after small amounts had been given; there was a concomitant increase in gastric acidity. Except in 3 instances in which massive hemorrhage necessitated operation, the ulcers healed completely.

GASTRIC NEOPLASMS

Polyps.—In a series of 4,000 gastroscopic examinations performed during an eight year period, gastric polyps were observed in 70 patients; men predominated 2 to 1; 70 per cent were more than 60 years of age. Anacidity was present in the majority of patients; however, the presence or absence of free acid and the appearance of the mucosa did not correlate closely with the symptoms or with the final diagnosis of the lesion.[102] A series of 20 benign, nonepithelial tumors of the stomach included 12 leiomyomas, 5 fibromas, 2 lipomas and 1 neurofibroma.[103]

Leiomyosarcoma.—Of 16 patients with leiomyosarcoma of the stomach, 4 are alive three months to four years after operation; 2 have survived more than five years.[104]

Spindle Cell Tumors and Sarcoma.—Spindle cell tumors of the gastrointestinal tract were found in 0.67 per cent of 12,000 necropsy

100. Palmer, E. D.: The Gastroscopic Picture in Post-Irradiation Gastritis, Am. J. Roentgenol. **60**:360, 1948.

101. Kurthi, L.: The Diagnosis and Treatment of Gastric and Duodenal Ulcers of Syphilitic Origin, Orvosok lapja **4**:586, 1948.

102. Hardt, L. L.; Steigmann, F., and Milles, G.: Gastric Polyps, Gastroenterology **11**:629, 1948.

103. Rabinovitch, J.; Grayzel, D.; Sawyer, A. J., and Pines, B.: Benign Nonepithelial Tumors of the Stomach, Arch. Surg. **58**:529 (April) 1949.

104. Marvin, C. P., and Walters, W.: Leiomyosarcoma of the Stomach, Arch. Surg. **57**:62 (July) 1948.

protocols. Nine per cent were located in the esophagus, 65 per cent in the stomach, 17 per cent in the small intestine and 9 per cent in the large intestine. Thirty-three per cent of the esophageal tumors and 36 per cent of the gastric tumors were malignant.[105]

Lymphosarcoma.—Hematopoietic neoplasms involve the stomach with greater frequency than is generally recognized; routine gastroscopic examination of patients with hematopoietic neoplasms is advocated.[106] Three types of involvement are noted gastroscopically: minute nodules in the mucosa, small masses in an abnormal mucosa and ulceration. Roentgen therapy or administration of nitrogen mustards had little or no effect on the gastric involvement. Of 11 primary gastric lymphosarcomas, 3 "five year cures" are reported.[107]

GASTRIC CANCER

Experimental Observations.—Silk threads containing methylcholanthrene produced new growths when embedded in the wall of the rat's stomach.[108] Inflammation, ulceration and sinuses lined with mucous cells in acinar fashion developed within two weeks. After thirty-five days, some of the new adenomas beneath the muscularis mucosae were transformed to adenocarcinoma, destroying reticulin barriers around the sinus. This transformation took place only when the mucous cells beneath the muscularis mucosae were in prolonged contact with the carcinogen. Carcinogen placed in the lumen of the stomach for comparable periods of time failed to produce malignant transformations.

Aqueous mineral oil emulsions, containing either methylcholanthrene or dibenzanthracene, were given instead of drinking water to mice. Squamous cell carcinoma of the forestomach was induced by methylcholanthrene in a large number of some strains of mice, whereas dibenzanthracene induced few such tumors. Malignant dyskeratosis of the forestomach was brought about with methylcholanthrene and dibenzanthracene in all but one strain. Few carcinomas and precancerous lesions were induced in the small intestine, in contrast to the results in previous experiments in which olive oil emulsions were used.[109]

105. Palazzo, W. L., and Schulz, M. D.: Spindle-Cell Tumors of the Gastrointestinal Tract, Radiology **51**:779, 1948.

106. Paul, W. D., and Hendricks, A. B.: Involvement of the Stomach in Malignant Lymphoma, Gastroenterology **11**:854, 1948.

107. Spellberg, M. A., and Ziven, S.: Lymphosarcoma of the Gastrointestinal Tract, Arch. Int. Med. **83**:135 (Feb.) 1949.

108. Howes, E. L., and de Oliveira, J. R.: Early Changes in the Experimentally Produced Adenomas and Adenocarcinomas of the Stomach, Cancer Research **8**:419, 1948.

109. Lorenz, E., and Stewart, H. L.: Tumors of Alimentary Tract in Mice Fed Carcinogenic Hydrocarbons in Mineral Oil Emulsions, J. Nat. Cancer Inst. **9**:173, 1948.

A review of the literature concerning hot foods as causative agents in gastric disease suggested to Davis and Ivy [110] that heat may be concerned in the causation of peptic ulcer, chronic gastritis and carcinoma of the stomach. Of these, the evidence seems strongest for thermal carcinogenesis, although even this point is not clearly established.

Histologic Observations.—Sixty-five cases of carcinoma of the cardio-esophageal junction were analyzed with reference to their possible histogenesis.[111] Certain adenoacanthomas and papillary adenocarcinomas were believed to have originated in the esophageal glands of the esophagus. An additional group of somewhat similar tumors, although possibly having origin in the same type of gland, may arise from "cardiac glands" of the esophagus or in the gastric mucosa.

Cancer of the stomach, with exception of cancer of the cardia, is associated with generalized chronic atrophic gastritis of moderate degree, present with equal intensity throughout the stomach without regard to location of the cancer. Gastritic changes accompanying carcinoma of the cardia are less pronounced than those associated with carcinoma of the body of the stomach.[112]

Spread of Pyloric Carcinoma.—Among 50 cases of pyloric carcinoma, invasion of the duodenum had occurred in 16.[113] Progression was mainly through the lymphatics of the duodenal wall; an anastomosis was demonstrated between the pyloric lymphatic plexuses and those of the first part of the duodenum. In a smaller proportion of cases the pyloric neoplasms invaded the duodenal tissues directly. Microscopically, the duodenal mucosa and the layer of Brunner's glands appeared to be the only tissues resisting the spread of tumor.

Gastric Secretion.—The volume, concentration and output of acid in the nocturnal gastric secretion are lower in patients with gastric carcinoma than in normal healthy persons or in patients with either duodenal or benign gastric ulcer.[114]

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110. Davis, R. E., and Ivy, A. C.: Thermal Irritation in Gastric Disease, Cancer **2**:138, 1949.

111. McPeak, E., and Warren, S.: Histologic Features of Carcinoma of the Cardio-Esophageal Junction and Cardia, Am. J. Path. **24**:971, 1948.

112. Guiss, L. W., and Stewart, F. W.: Distribution of Gastric Changes Accompanying Gastric Cancers in Various Locations, Arch. Surg. **57**:624 (Nov.) 1948.

113. Fodden, J. H.: Duodenal Spread of Pyloric Carcinoma, Brit. J. Cancer **2**:239, 1948.

114. Levin, E.; Kirsner, J. B., and Palmer, W. L.: The Nocturnal Gastric Secretion in Patients with Gastric Carcinoma: A Comparison with Normal Individuals and Patients with Duodenal Ulcer and with Gastric Ulcer, Gastroenterology **12**:561, 1949.

Hebbel and Gaviser[115] reviewed 284 cases of gastric carcinoma in which resection was done. Achlorhydria was uniformly present only with polypoid tumors, 3.2 per cent of the series. Free acid was present in 28 per cent of the demarcated ulcerating tumors, in 34 per cent of the partly demarcated, partly infiltrating tumors and in 41 per cent of the diffusely infiltrating tumors. In each group maximum acid values fell below 20 degrees in about one third of the cases and exceeded 20 degrees in about two thirds. Achlorhydria was present in 65 per cent of the entire series.

Laboratory Observations.—The sedimentation rate was increased in 80 per cent of patients with gastric carcinoma and was normal in 80 per cent of those with peptic ulcer.[116] One hundred and sixty patients with pernicious anemia, 5 of whom had gastric carcinoma, and 10 additional patients with gastric carcinoma were studied for incidence of blood group–specific substances in saliva and blood.[117] The occurrence of pernicious anemia and gastric carcinoma is not related to blood groups or Rh negativity. The percentage of patients secreting blood group–specific substances was approximately the same in those with gastric atrophy as in those with a normal mucosa.

Carbohydrate Metabolism.—Glycogen determination on biopsy specimens of the liver obtained at operation indicated that patients with gastric cancer fail to transform dextrose administered by stomach tube into hepatic glycogen.[118] The metabolic defect is corrected by the intramuscular injection of 10 to 30 ml. of an aqueous adrenocortical extract; insulin is without effect. The regulation of the peripheral blood sugar and the sensitivity to insulin are normal in patients with gastric cancer.

Plasma Proteins.—Electrophoretic studies disclose that in patients with gastric ulcer and carcinoma the hypoproteinemia is due to a decrease in albumin. In patients with gastric ulcer the other components are normal, whereas in those with carcinoma the gamma globulin and fibrinogen are somewhat increased. After resection of the tumor, these components return to normal within a few weeks.[119]

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115. Hebbel, R., and Gaviser, D.: The Relationship Between Gross Type of Gastric Carcinoma and Anacidity, Surgery **24**:512, 1948.

116. Rilliet, B.: The Blood Sedimentation Rate in the Diagnosis of Peptic Ulcer and Gastric Carcinoma, Rev. méd. de la Suisse rom. **68**:158, 1948.

117. Ladenson, R. P.; Schwartz, S. O., and Ivy, A. C.: Incidence of the Blood Groups and the Secretor Factor in Patients with Pernicious Anemia and Stomach Carcinoma, Am. J. M. Sc. **217**:194, 1949.

118. Young, N. F.; Abels, J. C., and Homburger, F.: Studies on Carbohydrate Metabolism in Patients with Gastric Cancer: Defective Hepatic Glycogenesis; Effects of Adrenocortical Extract, J. Clin. Investigation **27**:760, 1948.

119. Petermann, M. L., and Hogness, K. R.: Electrophoretic Studies on the Plasma Proteins of Patients with Neoplastic Disease: I. Gastric Cancer, Cancer **1**:100, 1948; II. An Acid Protein Present in the Plasma, ibid. **1**:104, 1948.

Homburger and Young[120] state that hypoproteinemia persists in patients with gastric cancer after operation, despite adequate body tissue repletion. Evidence is supplied that insufficient intake and excessive loss of protein are not responsible.[121]

Phosphorus Turnover.—Radioactive phosphorus in neutral solution was administered intravenously approximately thirty-six hours before resection of the stomach in 9 patients, 3 of whom had duodenal ulcer and 6 malignant tumors.[122] The rate of phosphorus turnover was at least 45 per cent higher in tumor tissue than in noncancerous tissue; the increased rate was limited to the cancer and was not demonstrable in the surrounding mucosa. In noncancerous stomachs there was no difference in the rate of turnover in areas where cancer is common, nor was the rate increased in a mucosa involved in atrophic gastritis. For phosphoproteins this rate was 124 per cent higher than normal; acid-soluble phosphorus turnover was essentially the same in cancerous and noncancerous tissue.

Roentgen Aspects.—A pilot five year study has been established to determine the efficiency of a photofluorographic process in detecting gastric carcinoma in a large segment of the population.[123] Little more radiation is given than that employed in conventional roentgenography. The apparatus utilizes a Patterson type E-2 screen and a Schmidt camera. The grid-screen-camera assembly is mounted beneath a horizontal roentgenographic table to permit the examination of patients in the recumbent position.

In 544 symptomless persons over the age of 50 whose gastric contents showed either achlorhydria or free acid of less than 30 units, 3 carcinomas and 19 presumably benign polypi were discovered by routine roentgen examination.[124] Kirklin and Hodgson[125] point out that it is impossible and impractical to have all persons over 40 years of age repeatedly undergo roentgen examinations of the stomach for carcinoma,

120. Homburger, F., and Young, N. F.: Studies on Hypoproteinemia: I. Hypoproteinemia in Patients with Gastric Cancer; Its Persistence After Operation in the Presence of Body Tissue Repletion, Blood **3**:1460, 1948.

121. Ariel, I.: The Nature of Post-Operative Hypoproteinemia in Patients with Gastrointestinal Cancer, Surg., Gynec. & Obst. **88**:185, 1949.

122. Schulman, J., Jr.; Falkenheim, M., and Gray, S. J.: The Phosphorus Turnover of Carcinoma of the Human Stomach as Measured with Radioactive Phosphorus, J. Clin. Investigation **28**:66, 1949.

123. Roach, J. F.; Sloan, R. D., and Morgan, R. H.: The Detection of Gastric Carcinoma by Photofluorographic Methods: I. Introduction, Am. J. Roentgenol. **61**:183, 1949; II. Equipment Design, ibid. **61**:188, 1949.

124. Rigler, L. G.: Roentgen Examination of the Stomach in Symptomless Persons, J. A. M. A. **137**:1501 (Aug. 21) 1948.

125. Kirklin, B. R., and Hodgson, J. R.: Carcinoma of the Stomach: Its Incidence and Detection, Am. J. Roentgenol. **60**:600, 1949.

in order that it may be detected before symptoms begin. Westing [126] and Moore [127] also believe that roentgenographic examinations of the stomach and bowel in symptom-free persons on a mass survey scale have no place in the cancer detection program.

Cytologic Diagnosis.—Ulfelder and his co-workers [128] describe an improved technic for the cytologic study of the gastric contents in patients suspected of having cancer of the stomach. Satisfactory cellular preparations were secured in 45 of 48 patients. Operation disclosed carcinoma of the stomach in 14, in 12 of whom the condition was diagnosed correctly by this method.

Richardson, Queen and Bishop [129] embedded in paraffin and sectioned material from 297 gastric aspirations obtained from 235 patients. Twenty-seven patients had proved cancer. In 13 the disease was originally diagnosed cytohistologically as cancer. On review of the sections, a total of 18 was given such a diagnosis. A false positive diagnosis of cancer was made in 2 patients. Twenty-four had proved ulcer, and the diagnosis was made from the microscopic examination in 20; a false positive diagnosis of ulcer was made in 3. Nine patients had proved gastritis; 6 had been given this diagnosis; a false positive diagnosis of gastritis was made for 3 patients. Eighteen patients proved to have no gastric lesions; this had been the diagnosis for 11. Six persons were called normal. The technic using embedded sections presents certain advantages over the smear technic, principally the concentration of material and the better preservation of cellular relationships.

Using the Papanicolaou method, the cell structure of the gastric juice of 278 patients was examined in 326 instances for the presence of neoplastic cells.[130] False positive smears were obtained in 14 per cent of patients without clinical evidence of neoplasm. In 43 instances in which there was histologic evidence of the absence of gastric neoplasms, the smears were negative in 72 per cent and indefinite or falsely positive in 28 per cent. In 20 cases with clinical evidence of neoplasm, the smears were positive in 40 per cent and negative in 60 per cent. In

126. Westing, S. W.: The Physician and the Detection of Presymptomatic Cancer, New York State J. Med. **49**:51, 1949.

127. Moore, S.: Mass Roentgenological Survey of the Gastro-Intestinal Tract to Detect Cancer of the Stomach, Am. J. Roentgenol. **61**:470, 1949.

128. Ulfelder, H.; Graham, R. M., and Meigs, J. V.: Further Studies on Cytologic Method in Problems of Gastric Cancer, Ann. Surg. **128**:422, 1948.

129. Richardson, H. L.; Queen, F. B., and Bishop, F. H.: Cytohistologic Diagnosis of Material Aspirated from Stomach; Accuracy of Diagnosis of Cancer, Ulcer and Gastritis from Paraffin-Embedded Washings, Am. J. Clin. Path. **19**:328, 1949.

130. Pollard, H. M.; Bryand, H. C.; Block, M., and Hall, W. C.: Diagnosis of Gastric Neoplasms by Cytologic Examination of Gastric Secretions, J. A. M. A. **139**:71 (Jan. 8) 1949.

41 cases with histologic evidence of neoplasm, 35 per cent of smears were positive and 65 per cent indefinite or negative.

Significance of Ulcerating Gastric Lesions After Gastroenterostomy.—The association of duodenal ulcer and benign gastric ulcer appears to be approximately twelve times commoner than the combination of duodenal ulcer and gastric carcinoma.[131] In 825 patients who had a gastroenterostomy stoma taken down and a partial gastrectomy performed, the complications for which surgical treatment was advised were jejunal ulcer, malfunctioning stoma, gastric ulcer and gastric carcinoma, in descending order of frequency. Of 41 gastric lesions developing after gastroenterostomy for duodenal ulcer, 27 per cent were gastric carcinoma and 73 per cent were benign gastric ulcers. Of 11 gastric lesions that developed or persisted after gastroenterostomy for gastric ulcer, 6 proved to be malignant and 5 benign ulcers.

Surgical Treatment and Results.—Of 377 patients with gastric cancer, 30.8 per cent survived resection and 7.4 per cent survived five years.[132] Fifty per cent of the five year survivors had had symptoms of more than one year's duration, as compared with 31 per cent of the initial group. Tumors were palpable in 40 per cent of the original group, as compared with 26.6 per cent of the survivor group. Nine of the survivors had polypoid tumor; 17 had an ulcerated sharply localized tumor, and 4 had an ulcerated tumor which was not sharply localized. No five year survivor had diffuse spreading carcinoma. Metastases were present in 23 per cent of five year survivors. In a comparative study of 30 patients who had lived five years or longer after resection of a gastric cancer and 30 patients who had died of local recurrence of metastases within one year after operation, morphologic factors associated with five year survival were sharp circumscription of the tumor, two special histologic types of cancer and a characteristic degeneration of tumor cells.[133] These studies indicate that the biologic type of the tumor is the most important determining factor in prognosis; the duration of symptoms appears to be of lesser significance.

The resectability rate for gastric cancer has improved from 2.9 per cent during the period 1916 to 1930 to 39.8 per cent between 1942 and 1946.[134] Of 75 patients surviving gastrectomy for cancer, 34.7 per cent

131. Gray, H. K., and Lofgren, K. A.: The Significance of an Ulcerating Lesion in the Stomach After Gastro-Enterostomy, Proc. Staff Meet., Mayo Clin. **23**:454, 1948.

132. Maimon, S. N.; Palmer, W. L., and Kirsner, J. B.: Prognosis in Gastric Cancer, Am. J. Med. **5**:230, 1948.

133. Steiner, P. E.; Maimon, S. N.; Palmer, W. L., and Kirsner, J. B.: Gastric Cancer: Morphologic Factors in Five-Year Survival after Gastrectomy, Am. J. Path. **24**:947, 1948.

134. Pack, G. T., and McNeer, G.: End Results in the Treatment of Cancer of the Stomach, Surgery **24**:769, 1948.

lived five years without recurrence. The operative mortality also has decreased greatly. The preoperative duration of symptoms apparently had no influence on the curability of those patients who have had gastrectomy for cancer. Five year cures for carcinoma in situ were 100 per cent, for ulcerocancer 33.9 per cent, for polypoid cancer 26.3 per cent, for infiltrating cancer 25 per cent and for annular cancer 22.7 per cent. Increasing grades of histologic malignancy were associated with decreasing rates of five year cure. Gelatinous carcinoma or mucocarcinoma is nearly always attended by a bad prognosis.

A total of 10,890 cases of gastric carcinoma was diagnosed at the Mayo Clinic from 1907 to 1938.[135] Gastric resection was performed in 25.5 per cent. Survival rates for patients with resections were five years or longer, 28.6 per cent; ten years or longer, 20.3 per cent; fifteen years or longer, 15.5 per cent; twenty years or longer, 10.4 per cent; twenty-five years or longer, 6.3 per cent.

Three hundred and forty-five cases of gastric cancer covering the twenty year period 1927 to 1947 are surveyed.[136] Resection was carried out in 131 patients, with a mortality of 10.7 per cent. Twenty-nine per cent of those in whom resection was done were alive after three years. After palliative operations, 6.8 per cent of the patients survived more than five years.

Of 1,473 patients with cancer of the stomach studied from 1936 to 1948, 94.7 per cent were operated on.[137] The gross operative mortality was 28.5 per cent. From the prognostic point of view, the invasion of the lymph nodes, the histologic nature of the tumor and the localization were important; local extension of the tumor had little prognostic significance. In early experience with total gastrectomy, the mortality exceeded 40 per cent, but in the last 67 cases it was 13.6 per cent.[138]

Ransom[139] reviews 68 cases of complete gastrectomy; the diagnoses were carcinoma, 59; gastric ulcer, 6; lymphosarcoma, 2, and neurofibroma, 1. There were 14 operative deaths (20.6 per cent); 40 of the remaining 54 patients died subsequently. Macrocytic anemia developed in 2 instances; microcytic anemia was more frequent. In one patient surviving nearly nine years, operation had demonstrated carcinomatous involvement of the regional lymph nodes, with neoplastic cells in the blood and lymphatic vessels.

135. Walters, W., and Berkson, J.: Results of Treating Carcinoma of the Stomach by Gastrectomy, Texas State J. Med. **45**:191, 1949.

136. Brynjulfsen, B. C.: Treatment of Cancer of Stomach During 20-Year Period, Nord. med. **39**:1402, 1948.

137. Haeffner, A.: Resultate der chirurgischen Behandlung des Magenkrebses, Krebsarzt **3**:217 and 248, 1948.

138. Lahey, F. H.: Total Gastrectomy, S. Clin. North America **29**:747, 1949.

139. Ransom, H. K.: Experiences with Total Gastrectomy, South. Surgeon **14**:801, 1948.

PEPTIC ULCER

Experimental Ulceration.—Berg [140] reviews in detail the literature dealing with the experimental production and treatment of peptic ulcer. According to Hanson and his associates,[141] increasing the rate of continuous administration of histamine above that which produces maximal gastric secretion increases the severity and rapidity of onset of ulceration in dogs, indicating that histamine exerts some additional effect in decreasing the resistance of the mucosa to the destructive effect of gastric juice. Three week old healed fundic and pyloric excisional ulcers in dogs did not break down and reulcerate during the administration of histamine, although ulcers developed in the adjacent normal mucosa of the pyloric portion of the stomach and duodenum.[142] The frequency, time of development, course, outcome and pathologic appearance of histamine-induced peptic ulcer in the guinea pig are unaffected by the administration of diphenhydramine. Thyroidectomy reduces the time required for perforation of histamine-induced peptic ulcer. Thiouracil-induced hypothyroidism did not influence the development of histamine-induced peptic ulcer.[143] The antihistamine, phenindamine tartrate (thephorin®), exhibited antiulcer effect in Shay rats and prevented gastric ulcer formation in rats given repeated injections of histamine; phenindamine tartrate reduced histamine-induced gastric secretion in dogs with Heidenhain pouches by approximately 30 per cent.[144]

Three groups of dogs were subjected to continuous intragastric infusion of a solution of hydrochloric acid containing 0.2 per cent pepsin.[145] In the first group metabolic acidosis was not controlled, and all dogs had peptic ulcer similar to that produced by 0.1 normal hydrochloric acid solution alone. In the second group the acidosis was controlled by the parenteral administration of 0.16 normal sodium bicarbonate solution and gastroduodenal ulcers did not develop. In

140. Berg, M.: The Experimental Production and Treatment of Peptic Ulcers: A Review of the Literature, Am. J. Digest. Dis. **16**:35, 1949.

141. Hanson, M. E.; Grossman, M. I., and Ivy, A. C.: Production of Gastroduodenal Ulcers in the Dog by Continuous Subcutaneous or Intravenous Administration of Histamine, Surgery **24**:944, 1948.

142. Hale, E. H., and Grossman, M. I.: The Resistance of Recently Healed Excisional Ulcer of the Stomach to Histamine-Induced Ulcer, J. Lab. & Clin. Med. **34**:228, 1949.

143. Watman, R. N., and Nasset, E. S.: Thyroid Activity and Resistance to Histamine-Induced Peptic Ulcer and to Acute Histamine Poisoning, Am. J. Physiol. **157**:216, 1949.

144. Lehmann, G., and Stefko, P. L.: The Action of Thephorin upon Histamine-Induced Gastric Secretion in Dogs and on Gastric Ulcer Formation in Rats, J. Lab. & Clin. Med. **34**:372, 1949.

145. Fogelman, M. J.; Grossman, M. I., and Ivy, A. C.: Further Studies on the Effect of Continuous Intragastric Infusion of Acid and Pepsin in Dogs, Surgery **25**:60, 1949.

the third group, the strength of the solution was increased to 0.15 normal hydrochloric acid, but the pepsin concentration was unchanged. Acidosis was prevented by the use of 0.3 normal sodium bicarbonate solution. Fifty per cent of these animals acquired either gastric or duodenal ulcerations. Thus, these observations are in contrast to the theory that the ulcerative action of acid-pepsin solutions is mainly dependent on their peptic activity.

The tendency for peptic ulcer formation was studied in dogs given injections of histamine in wax after total pancreatectomy, after ligation of the pancreatic ducts or after inducement of alloxan diabetes.[146] The 4 dogs with pancreatectomy and the 4 with ligation of the pancreatic ducts showed multiple ulcers, in contrast to the 4 control animals and the 4 dogs with alloxan diabetes in which a single ulcer or no ulcer resulted. These observations are interpreted as indicating the importance of the neutralizing alkaline secretions in the prevention of ulcer formation and also the desirability of returning these secretions to the proximal portions of the bowel to neutralize acid whenever the normal relationship of pancreatic ducts and duodenum is disturbed. As in the Mann-Williamson dog, peptic ulcers may develop in man when, in the treatment of pancreatic carcinoma, the bile duct is anastomosed to the jejunum distal to the gastroenterostomy opening and the pancreatic duct is ligated.[147] Three illustrative cases are described. The complication of peptic ulcer may be avoided by a surgical reconstruction which permits bile and pancreatic juice to pass over the gastroenterostomy stoma.

Resection of the antrum greatly decreased pouch secretion in dogs.[148] The average reduction in the twenty-four hour volume was 73 per cent, in the free acidity, 57 per cent and in the twenty-four hour output of hydrochloric acid, 84 per cent. These data indicate that, in the dog at least, the antrum is important in the chemical or hormonal phase of gastric secretion. Two groups of 10 dogs each were subjected to subtotal gastrectomy; an anterior type of gastrojejunostomy was performed, but in the first group the pyloric antrum was excluded and left intact, and in the second group the pylorus was resected.[149] In the first series, 9 of 10 dogs had marginal jejunal ulcers; in the second group, only

146. Poth, E. J.; Manhoff, L. J., and DeLoach, A. W.: The Relation of Pancreatic Secretion to Peptic Ulcer Formation, Surgery **24**:62, 1948.

147. Owens, F. M., Jr.: The Problem of Peptic Ulcer Following Pancreatectomy, Ann. Surg. **128**:15, 1948.

148. Woodward, E. R.; Bigelow, R. R., and Dragstedt, L. R.: Quantitative Study of Effect of Antrum Resection on Gastric Secretion in Pavlov-Pouch Dogs, Proc. Soc. Exper. Biol. & Med. **68**:473, 1948.

149. Schilling, J. A., and Pearse, H. E.: Re-Evaluation of the Role of the Pyloric Antrum in Marginal Peptic Ulcers, Surg., Gynec. & Obst. **86**:225, 1948.

2 of 10 animals showed ulcers. The authors conclude that the pyloric antrum definitely contributes to the incidence of marginal peptic ulcer.

Gastroduodenal ulcer is an occasional accompaniment of fracture and amputation of long bones.[150] The lesions can be produced in experimental animals by operative fracture or by curettage of the bone marrow; the incidence is decidedly increased by the concurrent administration of histamine. Similar ulcers can be produced by the intravenous injection of small amounts of fat; this also increases the susceptibility of animals to histamine-induced ulcer. Emboli of fat can be demonstrated in the submucosal and mucosal vessels in the stomach and duodenum in subjects with experimental fractures and in patients who died early after fracture of long bones; the fat disappears rapidly.

The gastric mucous cells of rats and dogs were stimulated by placing various substances into the stomach with both ends ligated; the materials included mustard oil and clove oil, from 0.5 to 2 per cent in corn oil, and eugenol in watery solutions, up to 10 per cent.[151] The animals in one group were killed from three to ten hours after operation. In another group, the ligatures on the stomach were removed after exposure to the irritant; the stomach was emptied and the wound closed. The same procedure was repeated several weeks later. Biopsies were taken before and after completion of the experiment. The action of the irritants on closed loops of small bowel and colon also was studied. Profuse macroscopic secretion of mucus was noted in the stomach without obvious histologic change. Deepening of the foveolae was first noted. Later, the most superficial segments of epithelium became detached, leaving only the deepest portions of the foveolae. If irritation ceased at this stage, immediate regeneration took place. Under a protective layer of debris and mucus, proliferation started at the bottom of the gastric pits. Growth of the cells from these areas restored the continuity of the surface epithelium. If destruction had not reached the bottom of the pits, it was followed by complete regeneration of the epithelial continuity in less than forty-eight hours. These observations suggest that the mucous barrier may be of considerable importance in the pathogenesis of gastric ulcer.

In rats maintained on rations excluding pantothenic acid, the duodenal mucosa became atrophic within one hundred to one hundred and twenty-five days; acute and chronic single or multiple ulcers developed

150. Friesen, S. R.; Merendino, K. A.; Baronofsky, I. D.; Mearo, F. B., and Wangensteen, O. H.: The Relationship of Bone Trauma to the Development of Acute Gastroduodenal Lesions in Experimental Animals and in Man, Surgery **24**:134, 1948.

151. Sanchez-Palomera, E., and Wangensteen, O. H.: Production of Irritative and Destructive Changes in the Gastric Mucosa Followed by Regeneration, Proc. Soc. Exper. Biol. & Med. **70**:427, 1949.

in 60 per cent of the animals, and a few of the lesions perforated.[152] Withdrawal of other vitamin B factors from the diet did not result in similar changes.

De Busscher [153] thinks that the arteriovenous anastomoses of the stomach play an important role in the genesis and course of peptic ulcer. On the other hand, the intra-arterial injection of contrast material into the resected ulcer-bearing stomach indicates that the appearance of the ulcer is not attributable directly to a vascular lesion per se. Subtotal devascularization of the stomach failed to protect dogs from Mann-Williamson ulcers.[154]

The survival time, epithelization of ulcer and deaths from ulcer were studied in 374 Mann-Williamson dogs subjected to various types of therapy.[155] Best results were reported with chorionic gonadotropin (antuitrin S®) therapy; benefit was obtained from extracts of normal male and female urine (parenteral administration) which did not contain the anterior pituitary-like hormone and from the follicle-stimulating hormone from pregnant mares' serum. Administration of posterior pituitary extract, a histidine monohydrochloride preparation (larostidin®), estrone and enterogastrone and vagotomy had no effect. Results with use of progesterone, solution of lactalbumin (aolan®), enterogastrone orally and extracts of heart muscle and of the urine from cancer patients and total gastrectomy were either slight or inconclusive.

Wener and Hoff [156] review extensively the evidence for the neurogenic concept of ulcer formation and conclude that two distinct but closely related processes must be considered: that which initiates the ulcers, and that which is responsible for the progression of the lesions to chronicity. Although vascular alteration leading to local tissue anoxemia and necrosis is the most important factor in the initiation of erosion and ulcers, the lesions produced have rarely, if ever, progressed to chronicity. The observations are interpreted to offer a physiologic basis for the neurogenic concept of ulcer formation and to reemphasize

152. Berg, B. N.; Zucker, T. F., and Zucker, L. M.: Duodenal Ulcers Produced on a Diet Deficient in Panthothenic Acid, Proc. Soc. Exper. Biol. & Med. **71**:374, 1949.

153. de Busscher, G.: Étude morphologique et considerations physiologiques sur la vascularisation de l'estomac, Acta gastro-enterol. belg. **11**:333, 1948; Vascular Etiology of Ulcus Rotundum Ventriculi from Viewpoint of Arterial Injections into Resected Stomach, Belg. tijdschr. geneesk. **4**:1115 and 1121, 1948.

154. Holm, B., and Mackay, A. G.: The Effect of Surgical Devascularization of the Stomach on the Production of Mann-Williamson Ulcers, Surgery **25**:446, 1949.

155. Salzstein, H. C.; Sandweiss, D. J.; Hill, E. J., and Hammer, J.: Results in Treatment of 374 Mann-Williamson Dogs, Gastroenterology **12**:122, 1949.

156. Wener, J., and Hoff, H. E.: The Neuro-Humoral Aspects of Peptic Ulcer Formation, Canad. M. A. J. **59**:115, 1948.

the importance of pronounced circulatory disturbances in the initiation of acute gastrointestinal lesions, ranging from mucosal hemorrhages to erosions and ulcers.

Daily injections of methacholine were given over a prolonged period to two groups of dogs.[157] Twenty-nine animals were given injections of 10 to 50 mg. of methacholine daily for two to one hundred and ninety-one days and received a total of 2 to 134 injections. Erosions or ulcers were observed in 12 of this group. Nineteen dogs were given methacholine in beeswax in doses of 25 to 125 mg. for periods of two to seventy-three days; gastric or duodenal erosions were observed in 8 of this group. The suggested sequence of events was vascular stasis, altered capillary permeability, hemorrhage, tissue anoxia and necrosis of mucosa. It should be noted that the lesions produced by methacholine were acute and multiple, in contrast to the chronic ulcer of man.

Young dogs were subjected to an operative procedure in which the inferior surface of the brain was exposed and a glass bead, approximately 6 mm. in diameter, placed intradurally between the anterior ends of the pedunculi, with resulting pressure on the tuber cinereum, corpora mammillaria and substantia perforata posterior.[158] Sixteen animals surviving the procedure were killed at postoperative intervals extending for approximately three months. The signs and lesions eventually obtained in some of the animals were: bleeding and formation of pus at the gingival margins with gray or black discoloration of the teeth, loss of teeth, ulceration of the buccal mucosa and lip margin, multiple duodenal ulcerations, frequent liquid stools, gross red blood in the stool, hemorrhagic mucosa and pinpoint ulcerations in the colon. In one dog an ileocecal intussusception with a large ileal ulcer developed at the head of the intussusception. Oral and intestinal lesions were noted in several instances in which the bead was found at autopsy deeply embedded in the lobus piriformis and not pressing on the hypothalamic area.

Gastric Secretion.—A definitely higher than normal gastric secretory response to 15 units of insulin given intravenously was noted in patients with duodenal ulcer.[159] The twelve hour nocturnal gastric secretion is essentially unchanged after the healing of duodenal ulcer.[160] The output

157. Wener, J.; Hoff, H. E., and Simon, M. A.: Production of Gastric and Duodenal Ulcers by the Prolonged Administration of Mecholyl, Gastroenterology **11**:904, 1948.

158. Schacter, M., and Schacter, R.: The Production of Visceral Lesions Following Attempted Chronic Irritation of the Central Nervous System, Canad. M. A. J. **60**:607, 1949.

159. Winkelstein, A., and Hess, M.: Effect of Insulin Hypoglycemia on Gastric Secretion in Duodenal Ulcer and Controls, Gastroenterology **11**:326, 1948.

160. Levin, E.; Kirsner, J. B., and Palmer, W. L.: Twelve-Hour Nocturnal Gastric Secretion in Uncomplicated Duodenal Ulcer Patients: Before and After Healing, Proc. Soc. Exper. Biol. & Med. **69**:153, 1948.

of hydrochloric acid in the nocturnal gastric secretion of 5 patients with recurrent or "intractable" peptic ulcer exceeded the general average for patients with duodenal ulcer.[161] The clinical course was characterized by severe pain and by serious complications, including hemorrhage, perforation and gastrojejunocolic fistula. The hypersecretion was not significantly reduced in the 4 patients so treated by large amounts of atropine or, in 3 instances, by enormous quantities of an enterogastrone concentrate. Roentgen irradiation of the fundus and body of the stomach effectively reduced gastric secretion in 1 patient, with subsequent healing of the ulcer. Irradiation diminished the output of acid temporarily in 1 patient and had no effect in 2. Section of the vagus nerves was accompanied in two instances with a pronounced decrease in acid and with healing of the ulcer. Gastric secretion was not permanently reduced in 2 patients, each of whom had undergone two vagotomies later demonstrated to be incomplete. The important role of "intractable hypersecretion" in "intractable" duodenal ulcer is thus further emphasized. The volume, concentration and output of acid in the fasting nocturnal gastric secretion are lower in patients with benign gastric ulcer than in patients with duodenal ulcer.[162] No significant difference was noted in the average volume secreted by patients with benign gastric ulcer and by normal persons; however, the concentration of hydrochloric acid and the output of acid were lower in patients with gastric ulcer. The output of gastric juice in patients with benign gastric ulcer is apparently continuous, although the secretion of hydrochloric acid is not continuous.

Appleby,[163] while accepting the concept that free hydrochloric acid may be a prerequisite in the development of peptic ulcer, expresses the opinion that "once the ulcer is soundly established and indurated, free hydrochloric acid is not the sole, nor possibly the main, cause of its persistence." It is pertinent to emphasize that the cases reported in the literature as demonstrating the coexistence of an active ulcer and achlorhydria have been inadequately studied. The secretory response of the stomach may undergo temporary phases of refractoriness.

Gastric Mucus.—The gastric mucus obtained from patients with peptic ulcer was observed to contain smaller amounts of histamine-like substances than were present in control subjects, and the ability of the mucus to absorb histamine was reduced.[164]

161. Kirsner, J. B.; Levin, E., and Palmer, W. L.: Observations on the Excessive Nocturnal Gastric Secretion in Patients with Duodenal Ulcer, Gastroenterology **11**:598, 1948.

162. Levin, E.; Kirsner, J. B., and Palmer, W. L.: The Nocturnal Gastric Secretion in Patients with Benign Gastric Ulcer, Ann. Int. Med. **30**:1020, 1949.

163. Appleby, L. H.: Surgical Consideration of the Nonmalignant Achlorhydric Stomach, J. Internat. Coll. Surgeons **11**:443, 1948.

164. Neumayr, A., and Schmid, J.: The Relation of Gastric Mucus to the Development of Ulcer, Gastroenterologia **74**:121, 1948-49.

Uropepsin.—Mirsky and his associates [165] describe a simple and reliable method for the measurement of uropepsin in the urine. The presence of gastric secretory activity is essential for the formation of uropepsin. Evidence is presented to indicate that uropepsin is derived from the direct secretion of pepsinogen into the blood stream by the secreting glands themselves and not from the reabsorption of pepsin from the lumen of the stomach. Healthy men excrete appreciable quantities of uropepsin at a fairly constant rate throughout the day and from day to day. This rate is not greatly influenced by the volume, specific gravity or acidity of the urine or by factors such as wakefulness, sleeping or ordinary exercise and the usual fluctuations in dietary habits. The ingestion of food does not appear to stimulate uropepsin excretion. The rate of uropepsin excretion is characteristic of the individual subject. Healthy men form a homogeneous group in regard to their rates of uropepsin excretion. Men with peptic ulcer excrete uropepsin at about twice the rate of healthy men. Uropepsin is absent from the urine of patients with pernicious anemia. Patients with gastric complaints but without peptic ulcer tend to resemble healthy men in regard to their excretion pattern.

Lysozyme.—The gastric content in peptic ulcer contains a higher than normal titer of lysozyme.[166] The low titer in peptic ulcer with obstruction is attributable either to dilution or to destruction of lysozyme by pepsin. In 5 patients the lysozyme titer decreased by 44 per cent after section of the vagus. The oral administration of large amounts of lysozyme in enteric-coated* capsules resulted in ulceration, hyperemia and edema in the stomach and small bowel of dogs.

Mechanism of Pain.—Epigastric tenderness in patients with chronic peptic ulcer was abolished when the splanchnic nerves were infiltrated with procaine hydrochloride. The exposed ulcerated stomach or duodenum was sensitive to pressure, to pinprick and to chemical stimulation. The nonulcerated stomach wall was insensitive to these stimuli. It is concluded that the epigastric tenderness was not due to irritation of the anterior parietal peritoneum by the ulcer but that the pain arose directly

165. Mirsky, I. A.; Block, S.; Osher, S., and Broh-Kahn, R. H.: Uropepsin Excretion by Man: I. The Source, Properties and Assay of Uropepsin, J. Clin. Investigation **27**:818, 1948. Broh-Kahn, R. H.; Podore, C. J., and Mirsky, I. A.: Uropepsin Excretion by Man: II. Uropepsin Excretion by Healthy Men, ibid. **27**:825, 1948. Podore, C. J.; Broh-Kahn, R. H., and Mirsky, I. A.: Uropepsin Excretion by Man: III. Uropepsin Excretion by Patients with Peptic Ulcer and Other Lesions of the Stomach, ibid. **27**:834, 1948.

166. Meyer, K.; Prudden, J. F.; Lehman, W. L., and Steinberg, A.: Lysozyme Activity in Ulcerative Alimentary Disease: I. Lysozyme in Peptic Ulcer, Am. J. Med. **5**:482, 1948.

within the ulcerated viscus.[167] Observations in more than 500 persons have shown that intragastric application of 0.1 normal hydrochloric acid produces pain only in patients with ulcer (or ulcerated cancer of the stomach).[168]

Gastric Ulcer.—Smith and Jordan [169] review a series of 600 patients with gastric ulcers. Malignant lesions were noted in 59 (9.8 per cent); in 47 of these the lesions were proved malignant histologically. The 541 patients with benign ulcers included 330 treated medically and 211 whose growth was proved benign by pathologic examination after resection. Operation was undertaken in 89 (42.1 per cent) of this group of 211 because of the diagnosis or suspicion of malignancy; in 70 (33.1 per cent) because of recurrence; in 21 (9.9 per cent) because of failure to heal; in 29 because of complications. One patient had a gastric polyp, and in one a large gastric ulcer which had not been discovered at roentgenographic examination was found at operation for cholelithiasis. Ten patients died during the period of hospitalization. The medically treated patients included 2 with malignant ulcers proved by postmortem examination six and twenty-three years after initial observation. In 97 patients who were treated without resection, recurrences were attributed to the continuation or resumption of smoking. In 20 patients who were maintained on medical management for two months to seven years and then operated on, the growth was found to be malignant. Resection of gastric ulcer is recommended when there is failure of complete healing within six to eight weeks as a maximum or when the lesion recurs.

Peptic Ulcer in Aged.—Among 155 cases of peptic ulcer in patients aged 60 years or more, the disease began after the age of 60 in 40 per cent.[170]

Peptic Ulcer in Children.—Several instructive cases are described.[171]

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167. Bentley, F. H.: Observations on Visceral Pain: Visceral Tenderness, Ann. Surg. **128**:881, 1948.

168. Gottsegen, V. G., and Hermann, B.: Die Salzsäureprobe in der Ulcusdiagnostik, Gastroenterologia **74**:270, 1948-1949.

169. Smith, F. H., and Jordan, S. M.: Gastric Ulcer: A Study of 600 Cases, Gastroenterology **11**:575, 1948.

170. Abramson, L.: Ulcer Diseases in the Aged, Nord. med. **40**:2206, 1948.

171. Abegg, W.: Ueber das Magen und Zwolffiingerdarmgeschur bei Kinden, Ann. pædiat. **171**:356, 1948. Chapman, H. L.: Duodenal Ulcer in a 13-Year Old Girl Associated with Emotional Strain, Canad. M. A. J. **59**:163, 1948. Pan, S. C., and Hsu, Y. T.: Duodenal Ulcer in Child of 2 Years: Case Report, Chinese M. J. **66**:274, 1948. Margolis, B.; Valdes-Dapena, M., and Boles, R. S.: Peptic Ulcer in Infancy, Gastroenterology **12**:489, 1949. Tedesco, B., and Kohn, R.: Un cas d'ulcère de la petite courbure gastrique chez un nourrisson de sept mons, Arch. d. mal. de l'app. digestif **37**:717, 1948.

Peptic Ulcer and Pregnancy.—This problem is elucidated further by two reports.[172]

Gastric Ulcer and Carcinoma.—Hoffman [173] analyzed 1,720 specimens of resected stomachs in an effort to determine the frequency of malignant changes in chronic simple gastric ulcers. So-called ulcer-cancers were considered to exist in 6.6 per cent of the 941 ulcers and in 8 per cent of the 779 carcinomas.

Curling's Ulcer (Duodenal Ulcer Due to Burns).—The introduction of penicillin is regarded as an important factor in the diminished incidence of this lesion.[174]

Gastroscopic Observations.—The gastric mucosa was normal in 82 of 107 patients with duodenal ulcer. Of 88 gastric ulcers demonstrated roentgenographically, 59 per cent were seen at gastroscopy.[175] Three additional ulcers were seen at gastroscopy which were not demonstrated roentgenographically. Of 35 "benign" ulcers as diagnosed by gastroscopy, the diagnosis was correct in 28, wrong in 1 and unproved in 6. Of 15 ulcers diagnosed malignant at gastroscopy, the diagnosis was correct in 9, incorrect in 4 and not proved in 2. Of 4 marginal ulcers visualized roentgenographically, one was seen at gastroscopy. The gastric mucosa in duodenal and in gastric ulcer may appear normal or present various types of inflammatory change; atrophy is more frequently associated with gastric ulcer; hypertrophic changes are commoner with duodenal ulcer.[176]

Antacid Therapy.—Mutch [177] states that it is not feasible to reduce acid continuously below the level of peptic activity by the administration of alkalis, unless the clinical conditions are exceptional. A combination of 50 per cent tribasic calcium phosphate, 50 per cent tribasic magnesium phosphate and 25 per cent silica is shown to be adequate. Beneficial results are ascribed to the use of a watery emulsion containing 40 per cent peanut oil and 10 per cent magnesium trisilicate [178] and to massive

172. James, D. W.: Peptic Ulcer During Pregnancy with a Report of a Case of Perforation, Brit. M. J. **2**:74, 1948. Carangelo, J., and Efstation, T. D.: Massive Gastric Hemorrhage in Pregnancy, Am. J. Obst. & Gynec. **56**:191, 1948.

173. Hoffman, M.: Carcinoma in Chronic Gastric Ulcers, Arch f. klin. Chir. **260**:570, 1948.

174. Braithwaite, F., and Beales, P. H.: Some Observations on Curling's Ulcer, Brit. J. Plast. Surg. **1**:284, 1949.

175. Dailey, M. E.: Gastroscopy in the Evaluation of Patients with Peptic Ulcer, Radiology **52**:796, 1949.

176. Ricketts, W. E.: Kirsner, J. B., and Palmer, W. L.: The Gastroscopic Appearance of the Gastric Mucosa in Peptic Ulcer, Am. J. M. Sc. **217**:542, 1949.

177. Mutch, N.: Antipeptic and Antacid Therapy with Special Reference to Adsorbent Complexes of Calcium and Magnesium Phosphates, Lancet **1**:859, 1949.

178. Tomenius, J., and Santesson, G.: Peanut Oil and Magnesium Trisilicate Mixture in Treatment of Peptic Ulcer Symptoms, Svenska läk.-sällsk. förhandl. **46**:372, 1949.

doses of bismuth subcarbonate.[179] Forty of 42 patients with duodenal or gastric ulcers obtained symptomatic relief in one to eight days after the use of anion exchange resins[180]; no data are presented concerning the effect of this substance on gastric secretion.

Tetraethylammonium Chloride.—Tetraethylammonium chloride prevented excessive nocturnal gastric secretion and acidity in 12 of 17 tests on patients with peptic ulcer.[181] A dose of approximately 20 mg. per kilogram of body weight given intramuscularly is usually effective if repeated at intervals of four hours. When given at such intervals, the compound inhibited excessive nocturnal gastric secretion and acidity in 6 of 7 patients with peptic ulcer. No serious toxic or side effects were observed. In 12 patients with active duodenal ulcer experiencing pain while receiving standard ulcer treatment, the distress was relieved by tetraethylammonium chloride given intramuscularly in doses up to 600 mg.; no alteration of gastric motility was noted by roentgen examination, but there appeared to be some diminution in secretion of free acid.[182] It is suggested that the relief of pain by use of the drug may be due to an alteration in the response of the circulation of the gastric mucosa, since the decrease in acidity was slight.

Antihistaminic Compounds.—Tripelennamine (pyribenzamine®) hydrochloride, given in doses of 100 mg. three times daily, had no effect on the gastric acidity or volume of secretion in patients with peptic ulcer.[183] Amidryl,® a compound identical to diphenhydramine hydrochloride, is reported to have reduced the gastric secretory response to histamine in 6 of 13 patients with peptic ulcer given 400 mg. of the drug daily.[184]

Enterogastrone and Other Extracts.—Enterogastrone was administered parenterally to 42 patients with proved chronic duodenal ulcers.[185]

179. Kemp, A. S.: Massive Doses of Bismuth Subcarbonate in Treatment of Ulcer, Nord. med. **40**:1979, 1948.

180. Weiss, J.: Treatment of Gastric and Duodenal Ulcers with Anion Exchange Resins, Rev. Gastroenterol. **15**:826, 1948. Weiss, S.; Espinal, R. B., and Weiss, J.: Therapeutic Application of Anion Exchange Resins in the Treatment of Peptic Ulcer, ibid. **16**:501, 1949.

181. Ferrer, J. M.: The Effect of Tetraethyl Ammonium Chloride on Gastric Secretion and Acidity in Peptic Ulcer, Surg., Gynec. & Obst. **87**:76, 1948.

182. Cayer, D.; Little, J. M., and Yeagley, J.: The Use of Tetraethylammonium Chloride in the Treatment of Patients with Peptic Ulcer, Gastroenterology **12**:219, 1949.

183. Hartman, S. A., and Moore, D. M.: The Effect of Tripelennamine Hydrochloride (Pyribenzamine) on the Gastric Acidity of Patients with Peptic Ulcer, Am. J. Digest. Dis. **15**:271, 1948.

184. Alsted, G.: Effect of Amidryl on the Gastric Secretion in Peptic Ulcer, Nord. med. **40**:1778, 1948.

185. Sandweiss, D. J.: Sugarman, M. H., and Lockwood, B. C.: Enterogastrone in the Treatment of Patients with Duodenal Ulcer, J. A. M. A. **138**:552 (Oct. 23) 1948.

The injections were given six, five or four times weekly for three months. The immediate clinical results were disappointing, since only 55 per cent of the patients had symptom-free intervals. The lowest percentage of relapses within one year occurred among those patients who followed the usual conservative dietary regimen.

Analysis was made in 46 cases in which a series of enterogastrone injections was given for duodenal ulcer and in which the course was followed for as long as five years after discontinuance of treatment; each patient served as his own control.[186] During a year of treatment 41 per cent of patients were symptom free and 46 per cent had fewer recurrences. At the end of the second year after the discontinuance of treatment, 40 per cent had fewer recurrences. The average of the longest symptom-free period in all patients was 0.3 year in the two years prior to therapy and 0.9 year after therapy. The authors conclude that the enterogastrone preparation probably contains an antiulcer substance tending to prevent recurrences in man. Favorable results with robuden, an extract of gastric and duodenal mucosa, are reported by several European writers[187]; the best results were obtained in early uncomplicated cases. It should also be noted perhaps that "good" results are more likely to be reported in the literature than unfavorable effects.

Protein Hydrolysates.—An enzymatic hydrolysate of protein was observed to be more effective than milk or casein in producing high p_H values of the gastric contents.[188] Gastric acidity was uniformly higher at ninety minutes than in the fasting contents after the ingestion of milk, casein or the hydrolysate. Gastric and duodenal bulb acidity was more effectively reduced by casein hydrolysate than by milk or milk and cream.[189] The superiority was less pronounced in the duodenal bulb than in the stomach. Secondary stimulation of acid secretion in the stomach followed feeding of casein hydrolysate. Buffer curves were determined in vitro for four commercial protein hydrolysates, whole fresh milk, aluminum gel, sodium bicarbonate, unhydrolyzed casein, dried

186. Ivy, A. C.; Littman, A., and Grossman, M. I.: Recurrence of Peptic Ulcer in Man as Affected by Treatment with an Enterogastrone Preparation, Gastroenterology **12**:735, 1949.

187. Mamie, M.: Robuden in the Treatment of Gastroduodenal Ulcer, Rev. med. de la Suisse rom. **68**:418, 1948. Neumann, H.: Beitrag zur Behandlung des Ulcus ventriculi und Ulcus duodeni in Früh- und Spätfällen, Schweiz. med. Wchnschr. **78**:1085, 1948. Holy, J., and Jelinek, M.: Experiences with Robuden Treatment of Gastric and Duodenal Ulcer, Gastroenterologia Bohema **2**:132, 1948.

188. Levy, J. S.: The Comparative Buffering Capacity of Intact and Pre-Digested Protein, Gastroenterology **11**:883, 1948.

189. Lopusniak, M. S., and Berk, J. E.: The Comparative Effects of Casein Hydrolysate, Milk and Milk-Cream on Gastric and Duodenal Bulb Acidity in Duodenal Ulcer Patients, Gastroenterology **11**:891, 1948.

whole milk powder and soy milk powder.[190] Whereas 300 Gm. of the most effective protein hydrolysate neutralized almost 5,500 cc. of 0.1 normal hydrochloric acid, this amount of acid was neutralized by 45 Gm. of sodium bicarbonate. It is concluded that the acid-neutralizing function of the protein hydrolysates is of major importance when they are administered orally in ulcer therapy. Various combinations of antacids and amino acids are considered helpful in therapy.[191]

Woldman and his collaborators[192] report no evidence of protein deficiency in 22 patients with peptic ulcer. A single dose of protein hydrolysate caused a decrease in the free acid and an increase in the total acid of gastric content. The period of neutralization varied with the quantity of hydrolysate administered. Multiple doses of 25 Gm. of protein hydrolysate every hour and a continuous drip of a 10 per cent solution ceased to neutralize free acid. A single dose delayed emptying time two hours. The ulcer pain did not disappear as rapidly in patients treated with protein hydrolysates as in patients given aluminum hydroxide gel. Kay and his associates[193] observed that the addition of a commercial extract of fresh hogs' stomachs to the diet of patients with peptic ulcer led to no symptomatic improvement. The addition of an enzymatic hydrolysate of fat-free whole milk, containing approximately equal parts of amino acids and readily assimilable carbohydrate, to the customary diet led to symptomatic improvement in only 2 of 12 patients, despite a gain in weight in all.

Hormonal Substances.—Increasing attention apparently is being directed to possible hormonal factors in the pathogenesis and treatment of peptic ulcer. Twenty-six patients with chronic duodenal and jejunal ulcer who had not responded to conventional treatment are reported to have benefited from administration of an extract of pregnant mares' urine; the period of observation was twenty months.[194] The intragastric

190. Samis, S. M., and Hollander, F.: Acid-Neutralizing Power of Several Protein Hydrolysates and Other Substances Used in Ulcer Therapy, Gastroenterology **12**:665, 1949.

191. Rossien, A. X.: Treatment of Gastroduodenal Peptic Ulcers with Protein Hydrolysate and a Non-Reactive Aluminum Hydroxide Preparation, Rev. Gastroenterol. **16**:34, 1949. Gonzalez, G. J. M.: Treatment of Peptic Ulcer with Amino Acid, Hispan. med. **5**:295, 1948. Bechelli, R.: Long Term Results in 50 Patients with Gastroduodenal Ulcer Cured with Medical Treatment, Gazz. Sanit. **19**:181, 1948.

192. Woldman, E. E.; Fishman, D.; Knowlton, R. S.; Rousuck, A. A., and Stoner, W. C.: Evaluation of Protein Hydrolysate Therapy for Peptic Ulcer, J. A. M. A. **137**:1289 (Aug. 7) 1948.

193. Kay, A. W.; Jamieson, R. A., and Smith, W. E.: Hog-Stomach Extract and Casein Hydrolysate in Peptic Ulcer, Brit. M. J. **1**:519, 1949.

194. Page, R. C., and Heffner, R. R.: Oral Treatment of Chronic Duodenal and Jejunal Ulcer with an Extract of Pregnant Mares' Urine, Gastroenterology **11**:842, 1948.

administration of an extract of pregnant mares' urine (kutrol®) in quantities as large as 7.5 Gm. did not decrease the volume, free acidity or output of hydrochloric acid in the twelve hour nocturnal gastric secretion or in the continuous thirty-six hour secretion of patients with peptic ulcer.[195] Piccinini [196] presumes an adrenal-gonadal influence on the incidence of peptic ulcer and also refers to a masculine component common to female patients with peptic ulcer; deficiency in vitamin C and impairment of the adrenal cortex are regarded as causal factors in peptic ulcer. Bastenie and his co-workers [197] are of the opinion that the normal secretion of estrogens and gonadotropic hormone protects the gastric mucosa against the factors responsible for ulceration; the therapeutic action of the sex hormones and of desoxycorticosterone appears attributable to the steroid nature of the hormones. Adrenocortical hormone is regarded as of definite therapeutic value.[198] The intramuscular administration of 10 mg. of desoxycorticosterone acetate is believed to have facilitated the healing of a large gastric ulcer.[199] The use of large amounts of follicular hormones apparently did not yield striking results.[200] Administration of a powdered extract of the posterior lobe of the pituitary gland was ineffective in 6 patients with peptic ulcer.[201]

Miscellaneous Agents.—Edlen [202] regards atropine administration as ineffective. Others [203] consider the intravenous injection of bromides and atropine a valuable adjunct. Varying results are recorded with

195. Kirsner, J. B.; Levin, E., and Palmer, W. L.: Failure of an Extract of Pregnant Mares' Urine to Influence Gastric Secretion in Man, Proc. Soc. Exper. Biol. & Med. **69**:108, 1948.

196. Piccinini, M.: Eziologia e terapia delle forme ulcerative gastriche e duodenali, Minerva med. **2**:77, 1948.

197. Bastenie, P. A.; Desneux, J., and Kowalewsky, K.: Clinique, physiopathologie et thérapeutique endocrino-gastroduodenales, Acta gastro-enterol belg. 1949, supp. 111, 1949, p. 57.

198. Brandis, S.: The Ambulatory Treatment of Gastroduodenal Ulcer, Acta gastro-enterol. belg. **11**:311, 1948. Ackermann, W.: General Survey of the Medical (Non-Surgical) Methods of Treatment of Gastroduodenal Ulcers, Rev. méd. de la Suisse rom. **68**:402, 1948.

199. Le Cluyse: Ulcus et thérapeutique par la corticostérone, Acta gastro-enterol belg. **12**:414, 1949.

200. Wagner, A.: On the Hormonal Treatment of Ulcers, Klin. Med. **3**:217, 1948.

201. Kobulniczky, E., and Bunyor, E.: Die Ulcuskrankheit und das Hypophysen-Hypothalamus-System, Schweiz. med. Wchnschr. **78**:832, 1948.

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ergotamine tartrate,[204] licorice root extract,[205] vitamin E[206] and histamine.[207] A special pancreatic pepsin preparation also receives favorable comment.[208] Seven patients with prolonged and "intractable" attacks of ulcer were treated with injections of their own serum.[209] The pain is reported to have ceased in every patient after one or two injections. The serum of ulcer patients protected the gastric mucosa of rats against ulcer formation after ligature of the pylorus. Rapid healing of peptic ulcers was obtained in 13 patients treated with fresh cabbage juice; the juice is believed to contain an antipeptic ulcer factor (vitamin U), which prevents the development of histamine-induced peptic ulcers in guinea pigs.[210] The tremendous variety of reportedly effective therapeutic agents in peptic ulcer, continually being published each year, constitutes *prima facie* evidence that the cure for the disease remains yet to be found.

Roentgen Irradiation.—Roentgen irradiation of the acid-secreting portions of the stomach proved to be a useful adjunct in the treatment of peptic ulcer, the results being proportional to the reduction in gastric secretion.[211] There was no correlation between the effect of treatment and the age of the patient or the duration of the disease prior to irradiation. The achlorhydria varied in duration from a few days to as long as eight years. Healing of the ulcers occurred consistently with achlorhydria of three months' duration. Recurrence of ulcers was always preceded by reappearance of acid gastric secretion.

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(To Be Concluded)

News and Comment

GENERAL NEWS

American Heart Association Grants-in-Aid.—The American Heart Association has announced that applications for Research Grants-in-Aid, including grants to basic sciences, may be filed up to Dec. 15, 1950.

Grants-in-aid are available to nonprofit institutions possessing the requisite basic facilities for research and having the necessary experienced investigators on their staffs. They are designated for a specified program of research.

Information and application forms may be obtained from Dr. Charles A. R. Connor, Medical Director, American Heart Association, 1775 Broadway, New York 19.

NOTICES

Course in Diseases of Endocrine Glands.—The Michael Reese Hospital Postgraduate School will offer a course in Diseases of the Endocrines, Physiology and Diagnostic Methods, from Sept. 18 through 29, 1950. The course will consist of a balanced program of lectures and case demonstrations. The tuition is $100. Further information may be secured from Dr. Samuel Soskin, Dean, Michael Reese Hospital Postgraduate School, Twenty-Ninth Street and Ellis Avenue, Chicago 16.

Course in Allergy for Clinicians.—A course in allergy for clinicians will be given October 1950 to October 1951 by the University of Illinois Allergy Unit, Colleges of Medicine and Pharmacy, Chicago. The primary purpose of the course is to give physicians an understanding of those conditions which are usually classified as allergic, so that they can diagnose and treat them competently. The course emphasizes clinical aspects and also endeavors to give a well rounded theoretic background on which clinical knowledge is built. The curriculum includes courses on sensitization mechanisms, respiratory allergy, food allergy, preparation of allergens, acute infectious diseases, immunochemistry, botany and mycology.

The course in allergy is accredited for one year toward the formal training requirements of either the American Board of Internal Medicine or of the American Board of Dermatology and Syphilology. The course is approved for training under the G. I. Bill of Rights. Enrolment is limited to 6 students. The tuition for residents of Illinois is $300 and for nonresidents $600.

Book Reviews

Bone Marrow Biopsy. S. I. Leitner, M.D. Price, $8.50. Pp. 433, with 194 illustrations, 6 plates and 22 tables. Grune & Stratton, Inc., 381 4th Ave., New York 16, 1949.

This handsomely printed and illustrated book, of over 400 pages, deals with every phase of bone marrow biopsy. Chapters on technic are followed by sections on the findings in various disorders. The literature is extensively reviewed, and there are case reports, tables and charts. No phase of the subject seems to have escaped the author's scrutiny. This is doubtless the most comprehensive treatise yet published on the subject.

Psychosomatic Medicine. By E. Weiss and O. S. English. Second edition. Pp. 803. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London W.C. 2, 1949.

The second edition of this book contains the newer concepts of the problem. It is written in the usual style of textbooks on the subject. Unfortunately, it is verbose and many theories are repeated frequently. The first chapters are concerned with general problems in psychiatry, e. g., definitions, points of view, discussions of clinical states, methods of examination of the patient, plans for training in psychosomatic medicine and related subjects. The greater portion of the book is devoted to expressions in the organic systems of psychic disturbances. The volume should prove of value to those in the field as well as to students. It is an average work.

Cardiology. By William Evans, M.D., D.Sc., F.R.C.P. Price, $7.50. Pp. 330. Paul B. Hoeber, Inc., 49 E. 33rd. St., New York 16; 90 Great Russell St., London, W.C. 1, 1948.

When it comes to fine bookmaking we can well take a leaf from our English colleagues. Their high standards are exemplified in the present volume, which is beautifully printed on fine paper and superbly illustrated with many excellent charts, diagrams and reproductions of electrocardiograms and roentgenograms. The text is concise and, especially for the student, the simple and precise method of discussion will be found useful. The sections on therapy are however disappointingly brief and indecisive. The book illustrates well, however, the modern approach to the study of heart disease, and the reviewer will be glad to have it on his shelves.

The Biological Standardization of the Vitamins. By Katharine H. Coward, D.Sc. Second edition. Price, $5. Pp. 224, with 38 illustrations. Philadelphia: Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1948.

This book should be most useful to anyone interested in the use of biologic methods in nutritional studies. The first chapter gives an excellent and concise presentation of the general principles which govern procedures of biologic assay and should be essential reading for the novice in the field. The main portion of the book is devoted to detailed discussion of methods for the determination of vitamin A, thiamine, ascorbic acid, vitamin D and vitamin E. In each instance precise instruction is given on the planning of experiments, reference standards,

selection of animals, diets and evaluation of findings. Suggestions concerning the housing and care of animals are included. When several methods are available for measuring a given vitamin, they are compared and evaluated.

The importance of statistical treatment of findings is emphasized throughout the book, while the last four chapters deal more fully with statistical methods as applied to bioassay technics.

The author, who has drawn largely from her own extensive experience, gives many practical details in outlining experiments. Such information is most valuable but is seldom available in publications dealing with methodology. References to recent literature are few. However, the author aimed to stress basic principles underlying biologic determination of vitamins and included only technics which she knew were satisfactory. The book is highly recommended to anyone planning investigations which involve biologic methods.

Physiology in Diseases of the Heart and Lungs. By Mark D. Altschule. Price, $5. Pp. 368. Harvard University Press, Cambridge 38, Mass., 1949.

This monograph was written primarily for medical students who may and should be interested in abnormal clinical physiologic states. The discussions are brief but well supported by a fairly extensive bibliography. Unfortunately, some of the problems are discussed so briefly that the student may have difficulty appreciating the disturbances in physiology, e. g., the discussion of tissue pressure, the lymphatics and venous pressure in chronic congestive heart failure. The discussion of chronic cardiac decompensation occupies one-half the monograph and contains numerous observations on various physiologic aspects of congestive heart failure, but unfortunately no attempt is made to correlate these many observations. Of course, as the author indicates, this is difficult at this time, so he merely presents the findings reported. In general, the monograph is more a brief review of the literature than an interpretation of the many findings for experienced students. In spite of this shortcoming, the book should prove to be very useful to students, interns and even trained physicians.

Behandlung innerer Krankheiten. By Ferdinand Hoff. Fourth Edition. Price, 10.80 marks. Pp. 471. Georg Thieme, Karl Tauchnitzstr. 3, Leipzig C. 1 (Russian Zone); Diemershaldenstrasse 47, Stuttgart-O (American Zone); 1949.

This book is intended to be a therapeutic guide for the general practitioner in Germany. It is divided into twelve sections, which cover the subject in a systematic fashion. As a help to the reader, there are some marginal notes so that one can quickly find that portion of the treatment in which one is interested. There are a number of good tables, particularly those on various foods and their carbohydrate, protein and fat constituents. All these will certainly be of help to the practitioner in treating his patients.

As with any book which covers such a broad subject, there are a number of errors. One cannot help questioning the efficacy of Strophanthus in the treatment of coronary insufficiency without failure. Certainly in the treatment of the common cold the use of a "swallow" from a glass of water in which 1 drop of tincture of iodine has been mixed is a novel one. In the treatment of diabetic coma the author stresses the use of Strophanthus in "stimulating the circulation." Occasionally, throughout the book, there is emphasis on what one must hold to be antiquated methods of treatment. For example, the author considers venesection an important

therapeutic measure in the treatment of lobar pneumonia, but he does not believe in "routine" digitalization of every patient. In the treatment of acute glomerulonephritis, the author states that sweat baths are of real importance in relieving the kidneys of a certain amount of their function. There is no mention of any of the newer drugs in the treatment of typhus fever or of Malta fever, nor is there any mention of the use of tetanus toxoid in the prevention of tetanus.

At the end, the author allocates some 36 pages to a list of the medicaments to which he has alluded in the book, including the price of each drug. He states that this will perhaps be of assistance to the physician in determining what to prescribe and will help him to advise the patient of the cost of the medicine.

The book is now in its fourth edition. Certainly it is to be hoped that with the fifth edition the author will be able to make the necessary changes so that its contents will properly express modern medical thought.

Rational Medicine. By John W. Todd. Price, $6.50. Pp. 378. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1949.

The recent great emphasis on mechanical and laboratory aids in medical practice will naturally stimulate an occasional writer to stress the simple (and perhaps nowadays often forgotten) clinical principles of diagnosis and treatment. The present book comprises the writer's thoughts on practice in somewhat haphazard and unsystematic fashion. Much of what he says is trite, and there is no documentation; at many points the information given is not too precise. Nonetheless there is a field for simple discussions of this sort which should remind the student and doctor that the practice of good medicine is not all measurement and mathematics. The reviewer found the book good reading.

Rose's Laboratory Handbook for Dietetics. Fifth edition. By C. M. Taylor and G. MacLeod. Price, $5. Pp. 358. The Macmillan Company, 60 5th Ave., New York 11; Macmillan & Co., Ltd., 10 St. Martin's St., Leicester Sq., London, W.C.2, and 32-34 Flinders St., Melbourne, C.I; Macmillan Co. of Canada, Ltd., 70 Bond St., Toronto 2; 1949.

This book of Mary Swartz Rose served through its four earlier editions, as its title implied, as a vade mecum for dietitians and others who had to deal with the calculation of food values and food requirements in the planning of dietaries. It it well to have it continued and brought up to date in a fifth edition by incorporating much of the recently acquired quantitative data on food composition. The principal food tables, as revised, provide data not only on calorie values and values for protein, fat and carbohydrate but also values for calcium, iron, vitamin A, thiamine, ascorbic acid and riboflavin. The values are expressed not only per pound but per ounce, per hundred grams and in household measures. In addition, given in supplementary tables, are data on essential amino acids, copper, manganese, iodine, oxalic acid, vitamin D, niacin, biotin, choline, pantothenic acid, para-aminobenzoic acid, pyridoxine, and vitamin losses from cooking. The discussion of nutritional requirements is based so far as possible on the recommendations of the Food and Nutrition Board of the National Research Council. Included also are numerous other data, including height-weight-age standards, equivalents of weights and measures and others. The book will be useful to many.

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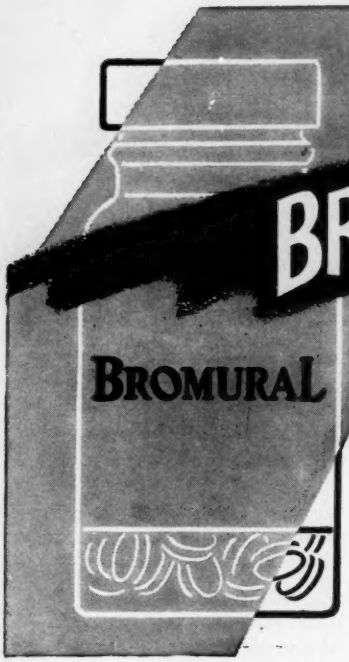

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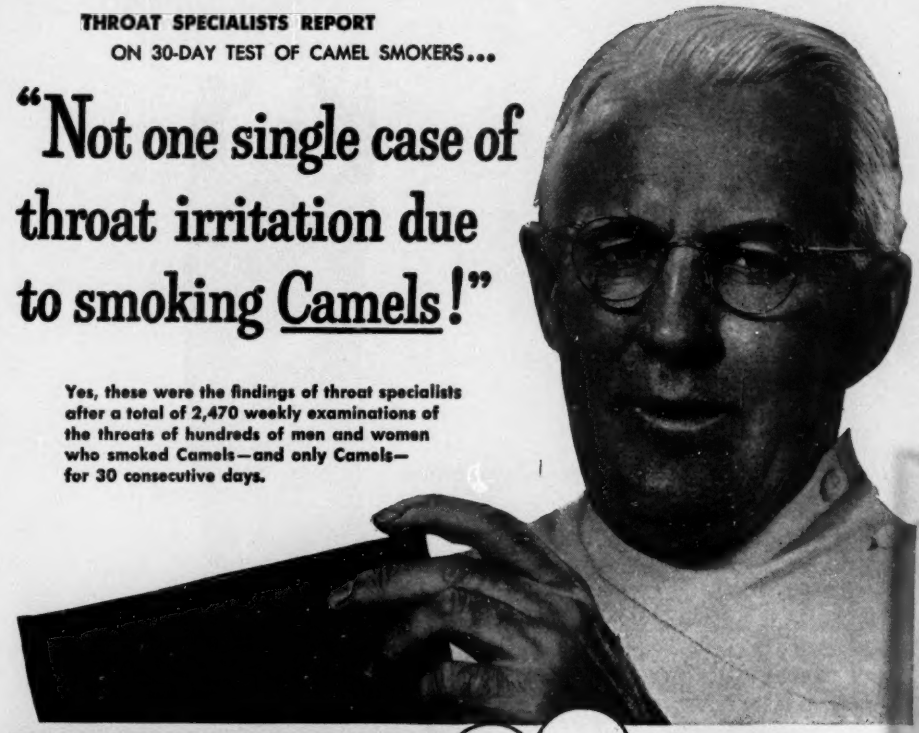

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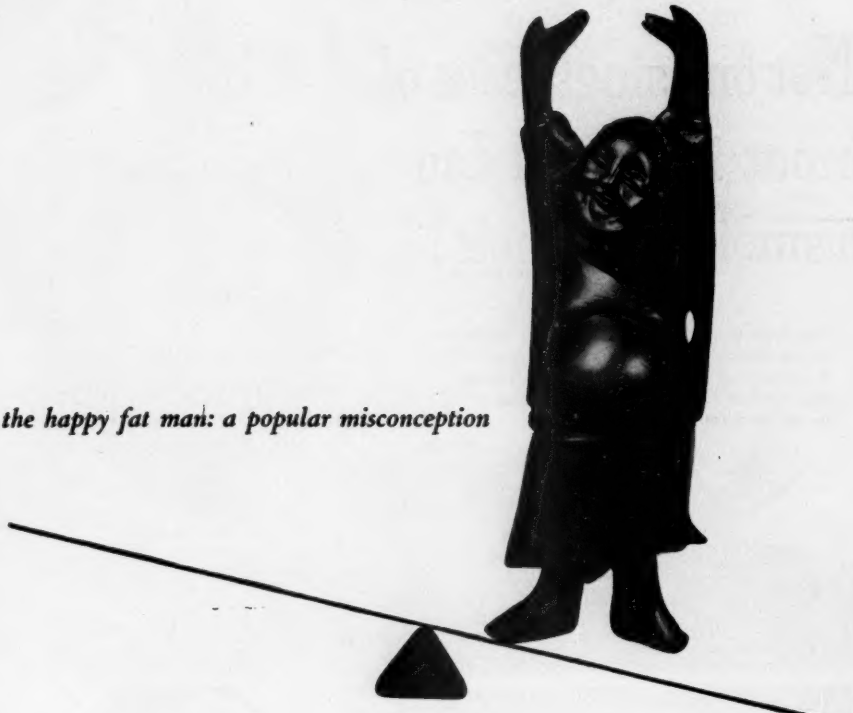

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